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(1) Kirby, W. M. M.; Waddington, W. S., & Doornink, G. M.: Antibiotics Annual, 1953-1954, New York, Medical Encyclopedia, Inc., 1953, p. 285.
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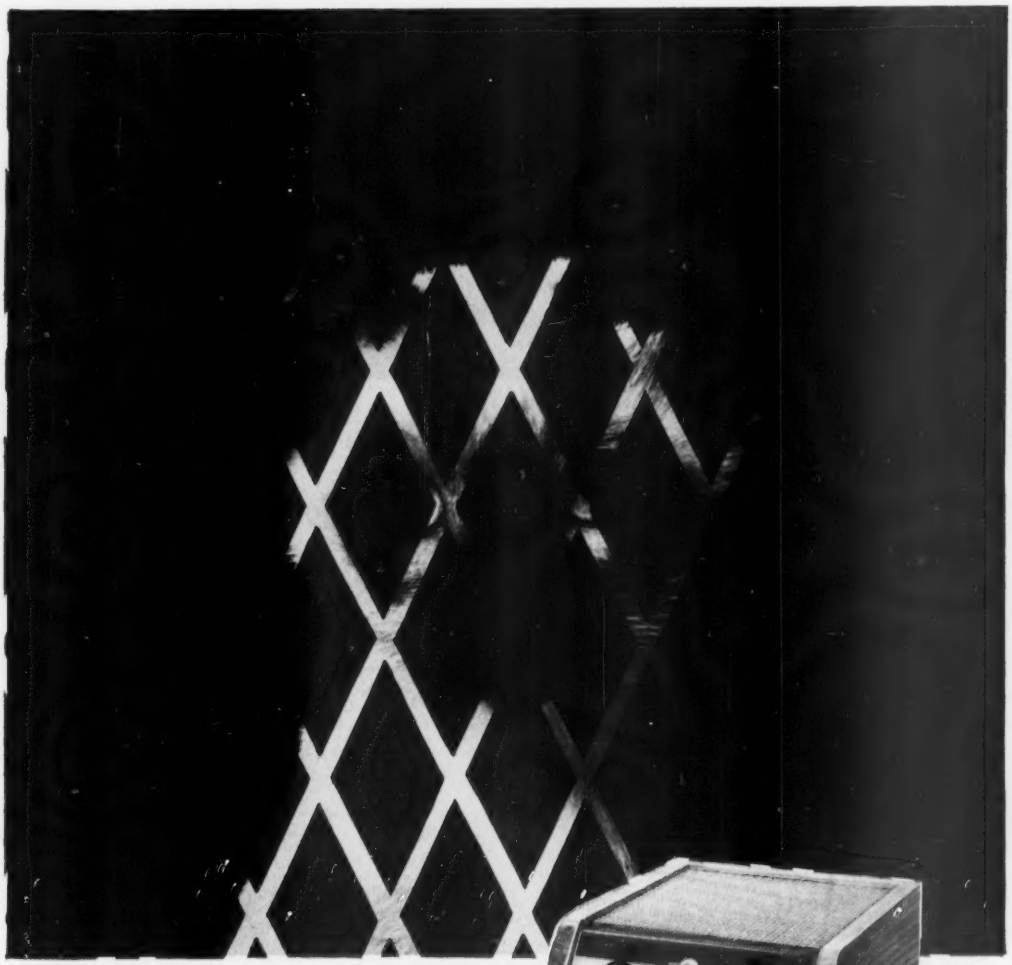

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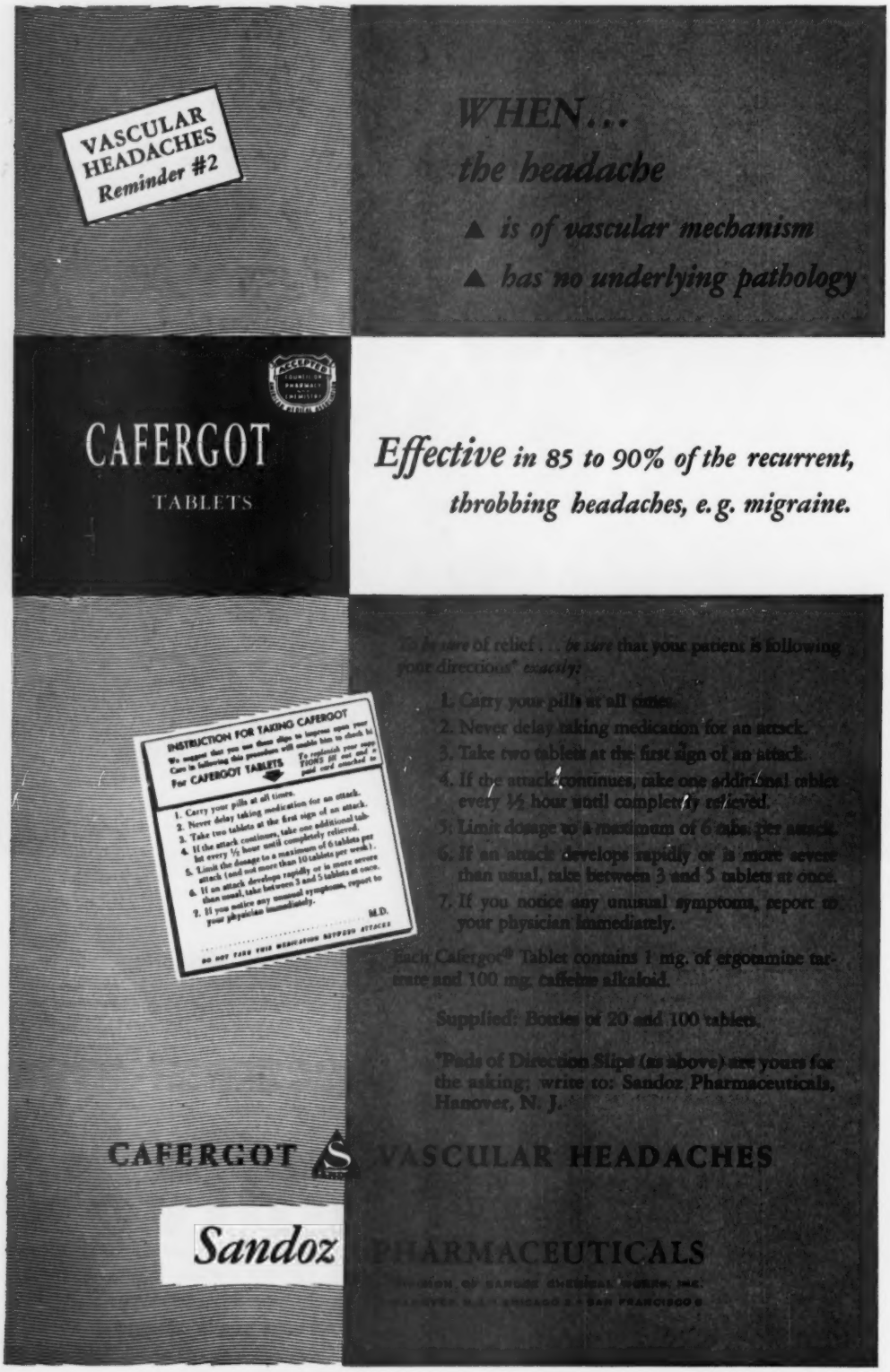
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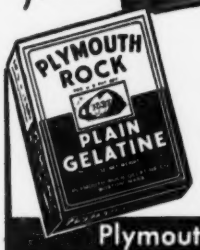

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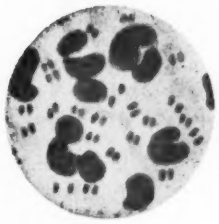

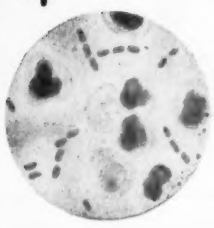

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1. Spink, W.W.: J.A.M.A. *152*:585 (June 13) 1953

2. Bush, W.L.: Southern M. J. *45*:870 (Sept.) 1952

3. Berkowitz, D.: Antibiot. & Chemo. *3*:618 (June) 1953

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Volume 251 SEPTEMBER 16, 1954 Number 12

ERYTHROBLASTOSIS FETALIS*

IX. The Problems of Stillbirth

FRED H. ALLEN, JR., M.D.,† LOUIS K. DIAMOND, M.D.,‡ AND A. RICHARDSON JONES, M.B., B.S. (LOND.)§

BOSTON

STILLBIRTH remains a major problem in erythroblastosis fetalis caused by Rh incompatibility, since about 20 per cent of the fetuses in these cases die in utero. The ultimate failure of all preventive methods that have been enthusiastically advocated in the past[1-4] illustrates the difficulty of interpreting the results of therapy in this condition. This difficulty arises from two principal factors: the great variability and unpredictability of erythroblastosis, and the fact that any method of treatment tends to result in a selected series of cases that may not be comparable with a previous, untreated series.

This study presents a nine-year survey of erythroblastosis fetalis at the Boston Lying-in Hospital (including the Richardson House, its private-ward division).

From 1945 to 1953, at the Boston Lying-in Hospital, 469 erythroblastotic babies were born to sensitized Rh-negative women. (Forty normal Rh-negative infants delivered of sensitized women are not counted in the totals.) Not included are a small number of Rh-positive babies who had a negative Coombs test and no signs of illness, and whose mothers had low anti-Rh titers. The figures are otherwise uncorrected. Included with the erythroblastotic deaths are a number of babies who apparently died of causes other than the hemolytic disease itself, such as hyaline-membrane disease. A few of the stillbirths that occurred outside the hospital early in pregnancy were included because the mothers had registered for delivery at the hospital. Every attempt was made to assure that the list is complete and representative.

*From the Blood Grouping Laboratory of Boston, the Boston Lying-in Hospital and the Children's Hospital and the Department of Pediatrics, Harvard Medical School.

Supported in part by Grant No. H-1227 (C) from the United States Public Health Service.

†Clinical associate in pediatrics, Harvard Medical School; associate hematologist, Children's Hospital; associate director, Blood Grouping Laboratory.

‡Associate professor of pediatrics, Harvard Medical School; associate chief, Medical Service, hematologist and director of Blood Bank, Children's Hospital; director, Blood Grouping Laboratory.

§Research associate in pediatrics, Harvard Medical School; research associate in hematology, Children's Hospital; associate director, Blood Grouping Laboratory.

NATURAL HISTORY OF ERYTHROBLASTOTIC STILLBIRTH

Table 1 shows the outcome from year to year. Stillbirths averaged 23 per cent in this period. This is somewhat higher than would have occurred if 36 per cent of the patients had not been referred because of previous erythroblastosis and if 33 per cent of their babies had not been stillborn as compared with only 17 per cent in those not referred. The 23 cases listed as "neonatal deaths with hydrops" were, for practical purposes, equivalent to stillbirths, though not customarily so listed. There was some variability from year to year, which is commented on below.

Table 2 correlates the two most important variables — past history and maternal titer — with the outcome in the 469 cases. Referred and nonreferred cases are listed separately, principally to show that the worse prognosis in the referred patients is related to the fact that they had higher titers (especially in the range of 256 to 512) than the nonreferred group, as well as worse past histories. The last column of Table 2 (headed "Totals") consists of the figures that relate past history to outcome, and it is seen that the frequency of stillbirth was much higher (56 per cent) when there was a history of previous stillbirth than when there was no previous erythroblastosis and no transfusion of Rh-positive blood (9 per cent). Sensitization by transfusion carries a fairly high risk of stillbirth (29 per cent), but Rh-negative babies are more frequent in this group. The last five rows of figures at the bottom of Table 2 relate the outcome to the maternal anti-Rh titer. The stillbirth rate was 48 per cent when the maternal titer was 1:1000 or higher and only 4 per cent when the maternal titer was 1:8 or lower.

In spite of the poor over-all prognosis in cases in which there has been a previous bad outcome, the outlook is not so bad as has been assumed by some writers, for 48 per cent of such cases resulted in live-born babies without hydrops. And in spite of the increased risk with high maternal titer, 59 per cent of the babies born to mothers with a titer of 1:64 or

higher were liveborn without hydrops. Even when the titer was 1:256 or higher 47 per cent were liveborn without hydrops (these figures were derived from the data in Table 2).

The figures in the main body of Table 2 indicate the effect of titer and past history on outcome. When the titer was 1:256 or higher and a previous baby had died 69 per cent were stillborn, and another 14 per cent were hydropic. Even here, though, 6 of 35 infants (17 per cent) were in good condition at birth, and the 1 in whom kernicterus developed would have recovered with the best present-day treatment.[5] With a maternal titer less than 1:64 and no previous history 80 of 82 infants were liveborn without hydrops. Our recent experience with patients in this category has shown a total fetal and newborn loss of only about 5 per cent.

Table 3 gives the fetal age at death in 108 erythroblastotic stillbirths and 23 cases of hydrops and relates this to the past history and titer. In cases with a past history of stillbirth or of infant death within twelve hours of delivery more than half the current stillbirths occurred before thirty-three weeks' gestation. With a more favorable past history there were many more late stillbirths. It may be pointed out here that in the cases with previous stillbirth the mother had anti-Rh antibodies in her serum throughout pregnancy; many of the others either had no antibodies at all at the beginning of pregnancy or developed a much higher titer during the latter part of their pregnancy. In other words, when the titer is low at the beginning of pregnancy the conditions that result in stillbirth may not develop until the last few weeks of pregnancy. When there has been a previous stillbirth, however, the conditions that lead to stillbirth are usually present throughout pregnancy, and stillbirth is very likely to occur early. It is believed that miscarriages before about sixteen weeks are not caused by Rh sensitization.

There was a slight excess of male babies among the stillbirths, but it was not a significant one.

Cause of Erythroblastotic Stillbirth

It appears almost certain that anemia is the primary cause of intra-uterine death in erythroblastosis fetalis. It is a widely held opinion also that heart failure (high-output failure secondary to anemia) is the most frequent immediate cause of death as well as the principal cause of the extensive edema. Anemia is the result, obviously, of increased destruction of the red blood cells consequent to their having been coated by the antibodies formed by the mother, in addition to the failure of the infant to produce enough blood to keep up with the increased rate of destruction. It has been postulated that the fetus in whom severe anemia develops may not be making new red cells in amounts commensurate with the extensiveness of its hematopoietic tissue, but this has not yet been proved. Certainly, the rate of red-cell destruction is very rapid in these babies.

Prevention of Stillbirth

Prevention of severe anemia is the most important consideration, whether this is accomplished by lowering of the rate of red-cell destruction or increase in the production of red cells, or both. The rate of destruction could presumably be lowered if the maternal antibody level could be materially reduced, by

Table 1. *Outcome of Pregnancies of Sensitized Rh-(D)-Negative Women at the Boston Lying-in-Hospital (including Richardson House).*

Year	Rh-Negative Babies*	Rh-Positive Babies						
		Stillbirths	Neonatal deaths with hydrops	Deaths without hydrops†	Living and dead with kernicterus	Recovered without sequelae	Totals	Induced labor‡
								%
1945	2	8 (28%)	3 (10%)	3 (10%)	5 (17%)	10 (34%)	29	50
1946	1	11 (23%)	2 (4%)	2 (4%)	9 (19%)	23 (49%)	47	70
1947	6	10 (19%)	2 (4%)	5 (10%)	8 (15%)	27 (52%)	52	50
1948	2	13 (22%)	1 (2%)	4 (7%)	4 (7%)	36 (62%)	58	38
1949	3	17 (31%)	5 (9%)	2 (4%)	0	31 (56%)	55	26
1950	7	8 (15%)	2 (4%)	0	1 (2%)	43 (80%)	54	23
1951	11	15 (26%)	3 (5%)	0	0	40 (69%)	58	27
1952	6	20 (33%)	3 (5%)	4 (7%)	0	34 (56%)	61	34
1953	2	6 (11%)	2 (4%)	1 (2%)	0	46 (84%)	55	57
Totals		108 (23%)	23 (5%)	21 (4%)	27 (6%)	290 (62%)	469	40
Referred cases (36%)§		56 (33%)	13 (8%)	8 (5%)	13 (8%)	78 (46%)		
Cases not referred (64%)		52 (17%)	10 (3%)	13 (4%)	14 (5%)	212 (70%)		

*Not included in totals.
†All deaths except hydrops & kernicterus.
‡Induction of labor, or cesarean section, whether because of titer or for obstetric reasons.
§"Referred" case one in which 1st erythroblastotic baby born at another hospital.

neutralization or mechanical removal, or if the antibodies could be prevented from passing through the placenta. Conceivably, by some new mode of attack, maternal sensitization to the Rh factor might be prevented in the first place, or reimmunization during deficiency of some humoral factor, there might be hope of preventing the severe anemia by administration of that factor to the mother. Whether congestive heart failure in the fetus could be prevented or treated is still unknown and untried.

TABLE 2. *Outcome in 469 Cases of Erythroblastosis Fetalis Related to Maternal Titer and to History of Previous Pregnancies.*

Outcome of Previous Pregnancies	Outcome of Present Pregnancy	Pre-partum Maternal Titer of Anti-D*															
		1000 & over		256-512		64-128		16-32		1-8		Unknown		Sub-totals		Totals	
		nr†	r†	nr	r	nr	r	nr	r	nr	r	nr	r	nr	r		
One or more erythroblastotic stillbirths	Stillbirth	2	3	3	12	3	8	1	6	0	1	1	0	10	30	40	(56%)
	Hydrops, with death	1	1	0	3	0	3	0	1	0	0	1	1	2	9	11	(15%)
	Death without hydrops	0	0	0	0	0	1	1	1	0	0	0	0	1	2	3	(4%)
	Kernicterus‡	0	0	0	1	0	0	0	1	0	2	0	0	0	4	4	(6%)
	Recovery	0	0	1	3	1	2	1	4	0	2	0	0	3	11	14	(19%)
One or more erythroblastotic deaths before 12 hr.; no stillbirths.	Stillbirth	1	0	1	1	0	4	0	0	0	0	0	0	2	5	7	(44%)
	Hydrops, with death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—
	Death without hydrops	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	(6%)
	Kernicterus‡	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—
	Recovery	0	0	0	0	1	3	1	2	1	0	0	0	3	5	8	(50%)
One or more erythroblastotic deaths after 12 hr.; no stillbirths or deaths before 12 hr.	Stillbirth	0	1	0	0	2	2	1	1	0	0	0	0	3	4	7	(32%)
	Hydrops, with death	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	(5%)
	Death without hydrops	0	0	0	0	0	0	1	0	0	1	0	0	1	1	2	(9%)
	Kernicterus‡	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—
	Recovery	0	0	1	0	3	1	1	4	0	2	0	0	5	7	12	(54%)
One or more kernicteric babies; no stillbirth or erythroblastotic death without kernicterus.‡	Stillbirth	0	0	2	3	2	3	0	1	0	0	0	1	4	8	12	(30%)
	Hydrops, with death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—
	Death without hydrops	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	(3%)
	Kernicterus‡	0	2	0	0	0	1	0	2	0	1	1	0	1	6	7	(17%)
	Recovery	0	0	0	4	0	4	2	5	0	5	0	0	2	18	20	(50%)
One or more previous erythroblastotic babies; all recovered.	Stillbirth	1	1	1	3	2	3	4	1	0	1	1	0	9	9	18	(16%)
	Hydrops, with death	1	0	2	2	1	1	0	0	0	0	0	0	4	3	7	(6%)
	Death without hydrops	0	0	0	0	1	1	0	2	1	0	0	0	2	3	5	(4%)
	Kernicterus‡	0	0	0	0	0	1	0	0	1	2	0	0	1	3	4	(4%)
	Recovery	1	0	4	8	13	12	16	11	8	6	1	0	43	37	80	(70%)
Sensitized by transfusion of Rh-positive blood; no erythroblastotic babies.	Stillbirth	1		3		1		3		0		1		9		9	(29%)
	Hydrops, with death	0		0		2		0		0		0		2		2	(6%)
	Death without hydrops	0		0		0		1		0		0		1		1	(3%)
	Kernicterus‡	0		0		1		0		0		0		1		1	(3%)
	Recovery	1		2		6		5		3		1		18		18	(58%)
No previous erythroblastotic babies; not sensitized by transfusion.	Stillbirth	3		3		6		0		1		2		15		15	(9%)
	Hydrops, with death	0		0		1		1		0		0		2		2	(1%)
	Death without hydrops	0		2		1		2		1		2		8		8	(5%)
	Kernicterus‡	1		0		5		1		1		3		11		11	(6%)
	Recovery	6		12		37		47		28		8		138		138	(79%)
Subtotals	Stillbirth	8	5	13	19	16	20	9	9	1	2	5	1	52	56		
	Hydrops, with death	2	1	2	5	4	5	1	1	0	0	1	1	10	13		
	Death without hydrops	0	0	2	0	2	3	5	3	2	1	2	1	13	8		
	Kernicterus‡	1	2	0	1	6	2	1	3	2	5	4	0	14	13		
	Recovery	8	0	20	15	61	22	73	26	40	15	10	0	212	78		
		(nr+r)		(nr+r)		(nr+r)		(nr+r)		(nr+r)		(nr+r)					
Totals	Stillbirths	13	(48%)	32	(42%)	36	(25%)	18	(14%)	3	(4%)	6				108	(23%)
	Hydrops, with death	3	(11%)	7	(9%)	9	(6%)	2	(2%)	0	—	2				23	(5%)
	Death without hydrops	0	—	2	(3%)	5	(4%)	8	(6%)	3	(4%)	3				21	(4%)
	Kernicterus‡	3	(11%)	1	(1%)	8	(6%)	4	(3%)	7	(10%)	4				27	(6%)
	Recovery	8	(30%)	35	(45%)	83	(59%)	99	(76%)	55	(81%)	10				290	(62%)
																469	

*Highest pre-partum anti-D (anti Rh_0) titer by albumin technic.
†nr = not referred; r = referred.
‡Includes deaths when associated with kernicterus.

pregnancy of the already sensitized woman might be blocked. Perhaps more likely of achievement than any of these would be an alteration in the nature of the antibodies that would make them less likely to get through the placenta. Modification of the damaging effect of the antibody on the fetal red cells is another possible approach to the problem, either by interfering with the antibody-antigen combination or by decreasing the vulnerability of red cells after the antibody-antigen combination has taken place. If it can be shown that severe anemia is the result of a

Early Delivery

Delivery before term is, at present, the only known method of reducing the frequency of erythroblastotic stillbirth late in pregnancy. From Table 4 it can be seen that if all women had been delivered at about thirty-six and a half weeks, 37 of the 131 cases of stillbirth or hydrops might have been prevented — 7 in the group with past history of stillbirth or hydrops and 30 in the group without such a history. If only the pregnancies of those with a titer of 1:64 or

higher had been interrupted at thirty-six and a half weeks, 28 stillbirths and cases of hydrops might have been averted, and this would have meant interruption of pregnancy in about half the women and a possible fetal salvage of about 16 per cent in that group. It is noteworthy that most of the stillbirths that would have been prevented by such a policy are in the group with titer 1:64 or above but with no history of death or hydrops — interruption of pregnancy at thirty-six and a half weeks would have resulted in a fetal salvage of about 14 per cent of this group. Delivery at thirty-six and a half weeks in the group with titer of 1:64 or higher and a past history of stillbirth or hydrops would have prevented 5 stillbirths and 1 case of hydrops, for a fetal salvage of about 32 per cent of those so treated. Delivery at thirty-four and a half weeks of all mothers with a titer of 1:64 or higher and a past history of stillbirth or hydrops might have prevented the 13 stillbirths and 6 cases of hydrops that occurred later on in this group of 32. This is the one group of cases with a prognosis poor enough to justify fairly radical measures.

TABLE 3. *Relation of Fetal Age to Titer and Previous History in 131 Cases of Erythroblastotic Stillbirth and Hydrops.*

Gestational Age at Time of Death	Maternal Titer	Outcome of Current Pregnancy with Previous Erythroblastotic Stillbirth, or Death within 12 hr. of Birth		Outcome of Current Pregnancy with No Previous Stillbirth or Death within 12 Hr. of Birth	
wk.		Stillbirth	Hydrops, with death	Stillbirth	Hydrops, with death
17-20					
	256 & over	6		1	
	64-128	3		0	
	<64	3		1	
21-28					
	256 & over	5		4	1
	64-128	2		6	0
	<64	2		1	0
	Unknown	1		1	0
29-32					
	256 & over	3	0	1	1
	64-128	2	1	3	2
	<64	1	0	1	0
	Unknown	0	1	1	0
33-34					
	256 & over	2	0	6	1
	64-128	2	1	1	2
	<64	0	0	3	1
35-36					
	256 & over	4	4	1	1
	64-128	4	1	1	0
	<64	2	0	0	0
	Unknown	0	1	2	0
37 & over					
	256 & over	3	1	9	1
	64-128	2	0	10	2
	<64	0	1	7	0
	Unknown	0	0	1	0

The foregoing estimates are based on the assumption that babies delivered before the time of intrauterine death would not have been hydropic. It is thirty-six and a half weeks would have resulted in a fetal salvage of about 14 per cent of this group. Delivery at thirty-six and a half weeks in the group with titer of 1:64 or higher and a past history of stillbirth or hydrops would have prevented 5 stillbirths and 1 case of hydrops, for a fetal salvage of about 32 per cent of those so treated. Delivery at thirty-four and a half weeks of all mothers with a titer of 1:64 or higher and a past history of stillbirth or hydrops might have prevented the 13 stillbirths and 6 cases of hydrops that occurred later on in this group of 32. This is the one group of cases with a prognosis poor enough to justify fairly radical measures.

TABLE 4. *Outcome in 469 Cases of Erythroblastosis (1945-1953).*

Outcome	Cases with Past History of Stillbirth or Hydrops			Cases with No Past History of Stillbirth or Hydrops		
	Titer of 1:64 or higher	Titer less than 1:64	Pre-partum titer not known	Titer of 1:64 or higher	Titer less than 1:64	Pre-partum titer not known
Death before 33 wk.	22	6	2	19	3	2
Still alive at 33 wk.	37	19	2	167	171	19
Stillbirth or hydrops after 33 wk.	24(65%)	3(16%)	1	35(21%)	11(6%)	3
Death between 33 & 35 wk.	5	0	0	10	4	0
Still alive at 35 wk.	32	19	2	157	167	19
Stillbirth or hydrops after 35 wk.	19(59%)	3(16%)	1	25(16%)	7(4%)	3
Death between 35 & 37 wk.	13	2	1	3	0	2
Still alive at 37 wk.	19	17	1	154	167	17
Stillbirth or hydrops after 37 wk.	6(32%)	1(6%)	0	22(14%)	7(4%)	1
Total cases	59	25	4	186	174	21

our belief (but it is one most difficult to substantiate) that most infants who become hydropic in utero die shortly thereafter and that the infants delivered early would usually not be hydropic. It can be assumed, nevertheless, that some babies, delivered at any predetermined time, will be hydropic. We believe, however, that some if not most of the babies who were

born hydropic would have been in good condition if they had been delivered a week earlier. In the group with a past history of stillbirth or hydrops, 8 babies liveborn after thirty-four and a half weeks' gestation were hydropic.

Definite recommendations cannot yet be made regarding which women should be delivered early, or how early they should be delivered, beyond the statement that a certain number of stillbirths can presumably be prevented by this measure. When the husband is known to be heterozygous, delivery before thirty-seven weeks should not be recommended for fear of jeopardizing the life of an Rh-negative baby by prematurity. We do not ordinarily consider any but the most benign procedures in a case in which there are already 2 or more healthy children in the family. In deciding whether to terminate pregnancy before thirty-five weeks' gestation one must face the considerable increase in risk to the infant from prematurity. Perhaps most important of all, it is foolhardy in the extreme to practice early delivery of erythroblastotic babies unless exchange transfusions can be done promptly by an expert team, and repeated when necessary to prevent an excessive rise in serum bilirubin. Kernicterus becomes a frequent complication when the serum bilirubin exceeds 20 mg. per 100 cc., which it will nearly always do in untreated premature infants with erythroblastosis fetalis. Exchange transfusion with compatible blood greatly modifies the jaundice and bilirubinemia, and prevents kernicterus. In our experience about 25 per cent of the babies require a second exchange transfusion, and some have required a third or fourth to keep the serum bilirubin from exceeding 20 mg. per 100 cc. In our opinion, however, prevention of kernicterus is always possible.

Treatment by early delivery should be a matter of individual judgment, each case being considered in the light of previous history, maternal titer, Rh genotype of husband, availability of immediate exchange transfusion and safety to the mother. One will obtain worse results by early delivery without exchange transfusion than by doing nothing because of the high risk of kernicterus, as we found in our own clinic from 1945 through 1947.

Evaluation of Treatment

Whenever a method of treatment is tried it is important to have a simultaneous series of untreated cases for control, and to assure as far as possible that the two series are similar in all other respects. This is not easy. In any event it is essential to compare the treated cases with untreated ones, the previous history, the titer, the time at which treatment was started and the extent to which early delivery was used being taken into account.

To illustrate the method of analysis of clinical data in erythroblastosis 2 examples are discussed.

In Table 1 it is seen that in 1952 there were 20 stillbirths and 3 babies with hydrops out of a total of 61 cases. In 1953 there were only 6 stillbirths and 2 cases of hydrops among 55 cases. There is no question that the results in 1953 were superior, but can this be related to treatment? Analysis of the past histories shows that the number in each year with previous history of stillbirth was identical (15 per cent), whereas there were a few more cases in 1953 (62 per cent) with a previous erythroblastotic baby or transfusion of Rh-positive blood than there were in 1952 (57 per cent). If one were content to stop there, one might conclude that the effectiveness of the treatment in 1953 had been proved. However, since there was in fact no difference in treatment between the two years, except that induction of labor was practiced more frequently in 1953, one is obliged to go farther with the analysis unless the improved results are to be ascribed to good luck. Actually, the increased use of induction of labor, which was done somewhat earlier (though seldom before thirty-seven weeks' gestation) as well as more frequently, may have played a part in the better results, but one other variable needs to be explored — the maternal titer. Table 5, which compares the maternal anti-Rh titers in the two years, shows that the number with high titers was much greater in 1952. This is surely accidental, although such a discrepancy would be encountered but once in about 50 trials, by chance alone. It is fortunate that the 1953 group was not a treated group, and the 1952 group its control, for the data would have to be discarded because of the differences in the maternal titers.

Table 5. *Comparison of Maternal Anti-Rh Titer.*

Year	Titer Under 64 Units		Titer of 64 Units or Higher	
	No.	Percentage	No.	Percentage
1952*	12	20	48	80
1953*	22	41	32	59

*Pre-partum titer unknown in 1 case.

The second example, which illustrates an erroneous conclusion, is from the literature, being the data of Hunter[6] on cortisone therapy in Rh incompatibilities. After "treatment" of 67 sensitized women with cortisone stillbirth occurred in 6 of the infants, and neonatal death in 5. If the 9 normal, Rh-negative babies had been excluded, as they should have been, the recovery rate would have been 81 per cent, which is practically as good as our results in a series of similar size in 1953, and about the same as our results in 1950. Hunter claimed that his good results were due to the administration of cortisone but he started with the arbitrary and unwarranted assumption that 100 per cent stillbirths were to be expected in cases with a history of previous stillbirth.

It is also necessary to consider whether there is any

departure from random selection in his cases. This is the real crux of the matter. One must exclude from Hunter's series all cases in which the mothers were not under observation by seventeen weeks, since that is the gestational age at which stillbirths began to occur in the series at the Boston Lying-in Hospital. Since Hunter did not start treatment with cortisone until "the last trimester" we should allow him to include all cases in which he began to do tests of pregnanediol and 17-ketosteroid excretion at or before seventeen weeks of gestation. Unfortunately, his statement that these tests "were started around the 20th week" does not indicate how many, if any, were started as early as seventeen weeks. Furthermore, only "a large percentage of the mothers were studied by means of these excretion tests," and the data do not indicate which were not. There is no indication, therefore, that Hunter's series was a representative one. If he accepted any cases for treatment as late as the third trimester because of a past history of stillbirth it is virtually certain that other cases were not presented for treatment because by this time the babies had died. A glance at the Boston Lying-in Hospital series (Table 3) shows the fallacy of accepting patients "for treatment" at later than seventeen weeks' gestation if they have an unfavorable history. There is other evidence that Hunter's series was a selected one. At least 31 per cent of his patients had had stillbirths — not including the 4 with previous "miscarriages" — as against only 12 per cent in the nonreferred group at the Boston Lying-in Hospital. One can only guess how this distorted Hunter's data, since he offers no information on the matter. Finally, unless the number and time of early deliveries are indicated, it is impossible to allow for the very real effect of this measure on the frequency of stillbirth. In a properly controlled series the effect of early induction either in the treated group or in the controls could easily be removed by consideration of the status of the babies at a chosen gestational age somewhat younger than that at the earliest cesarean section or induction of labor. Hunter gives no data regarding the frequency or time of early induction. The only conclusion possible is that Hunter's published data give no justification whatever for his claim that cortisone has any value in the treatment of "Rh complications."[6]

Others who have used cortisone and ACTH[7-11] in attempted treatment of sensitized Rh-negative women have found them of no value.

A properly prepared report of a clinical trial should include a series of untreated controls, an explanation of how cases and controls were chosen and handled so as to assure that the only differences between them consist in the treatment itself, a listing of the possible variables that might affect the validity of the result and an analysis of these variables in both treated and untreated groups. If none of these points are covered the data may be worthless.

In this paper we have attempted to show the important variables in erythroblastosis that affect the stillbirth rate, and have presented such basic data as may be useful in the analysis of methods of treatment that may be tried in the future. The analysis of the published data on cortisone therapy does not *prove* that the hormone is worthless, but only that its value has not been demonstrated. It is considerably easier, in a condition as variable as erythroblastosis, to prove that something is of value than to prove beyond doubt that it is not. It is not unlikely that a really effective treatment will eventually be found because there are many points of attack on the problem, as suggested in the discussion of the prevention of stillbirth. Until such time, the judicious use of early delivery is the only method available.

The one disadvantage of early delivery is unfortunately an insuperable one. It cannot be used early enough (before thirty-three weeks) to prevent even half the stillbirths without causing more trouble in the way of prematurity than is prevented in the way of stillbirths. At the Boston Lying-in Hospital the regular use of early delivery in the years 1945, 1946 and 1947 resulted in such a large number of deaths and cases of permanent brain damage that it was almost completely abandoned for some time. Only within the last year or so has the increasing confidence in exchange transfusion, both for saving lives and for preventing brain damage, led once more to the cautious trial of early delivery as a means of preventing stillbirth. It will take several years, at least, to evaluate the combined use of early delivery and exchange transfusion. Nevertheless, it is better than no expedient at all, and certainly deserves a fair trial in properly chosen cases.

Summary and Conclusions

Data from nine years' experience at the Boston Lying-in Hospital are presented to show the relation of stillbirth to the important variables that affect the outcome in erythroblastosis fetalis. It is hoped that these data will be useful in the evaluation of methods of prevention that may be proposed in the future.

There are many possible approaches to the problem of preventing erythroblastotic stillbirths, but no treatment now known is of any value except for early delivery in selected cases, followed by prompt exchange transfusion.

There is no evidence that any drugs advocated to date, including cortisone, have any value in the prevention of erythroblastotic stillbirth.

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IMMUNIZATION OF ADULTS AGAINST DIPHTHERIA AND TETANUS*

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IMMUNIZATION against diphtheria and tetanus in childhood is now a well established procedure in Massachusetts as well as many other communities. The large majority of infants receive a solid basic immunity against these diseases through the standard application of triple vaccine (pertussis, diphtheria and tetanus). The Institute of Laboratories of the Massachusetts Department of Public Health has issued for the last three years twice as many doses of this preparation as the number of annual births in Massachusetts. The recommended procedure of booster immunization with the triple antigen at the time of entry into elementary school is widely followed.

Recent studies of the Massachusetts Department of Public Health,[1] in co-operation with local school departments, have led to a recommendation of further booster immunization of high-school students, 0.1 cc. of double antigen (diphtheria and tetanus) being used. It is hoped that this procedure, which is taking effect this year, will gain general acceptance.

Thus, with immunization now extended to the entrance of adulthood, there are reasons to consider the need for further immunization during adult life, and to discuss a positive proposal for its implementation. The main emphasis in this discussion is on local problems of this geographic area, but, assuredly, the problem has more than local interest.

The various aspects of adult immunization have been adequately covered in the literature. Some important papers are cited,[2-7] from which extensive reference to the problems can be obtained.

MORBIDITY AND MORTALITY IN MASSACHUSETTS

Diphtheria

Reported cases of diphtheria in Massachusetts show a decrease in total annual cases from around 8000 in the early 1920's (when toxin-antitoxin immunization started) to only 31 cases in 1953. The continued downward trend was interrupted by a flare-up of diphtheria in 1946-1949, with 300 to 400 cases annually. Childhood immunization was intensified after 1949, especially with the introduction of triple vaccine. It is pertinent to scrutinize the data for diphtheria in adults by comparison with that in children in the last decade and in previous periods. A crude summary, which is presented in Table 1, is based on official reports to the Massachusetts Department of Public Health.

TABLE 1. *Diphtheria in Adults and Children (Massachusetts, 1924-1953).*

PERIOD	AGE	NO. OF CASES ANNUALLY	NO. OF DEATHS ANNUALLY	CASE MORTALITY
	yr.			%
1924-1943	Under 15	1611	120.0	7.4
	Over 15	249	9.8	2.8
1944-1953	Under 15	134	7.9	5.9
	Over 15	86	7.6	8.8
Difference between periods	Under 15	Decrease of 12.0-fold	Decrease of 15.2-fold	Decrease of 1.3-fold
	Over 15	Decrease of 4.1-fold	Decrease of 1.3-fold	Increase of 3.1-fold

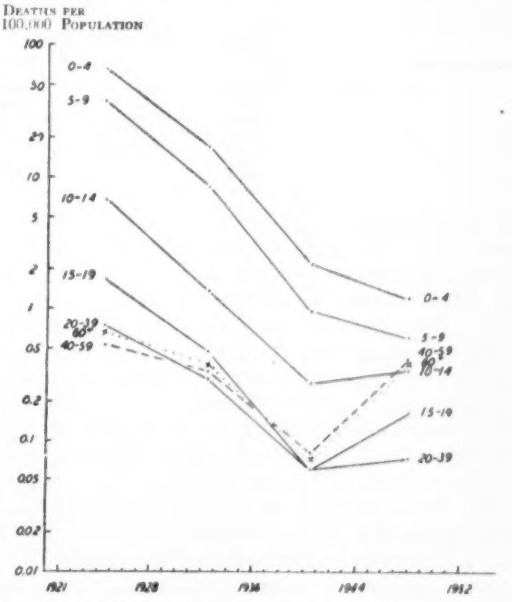

FIGURE 1. *Diphtheria Trends in Age-Specific Mortality in Eight-Year Periods (Massachusetts, 1921-1953).*

The decrease in cases, deaths and case mortality is not nearly as pronounced in adults as in children. Although adult cases dropped fourfold from the

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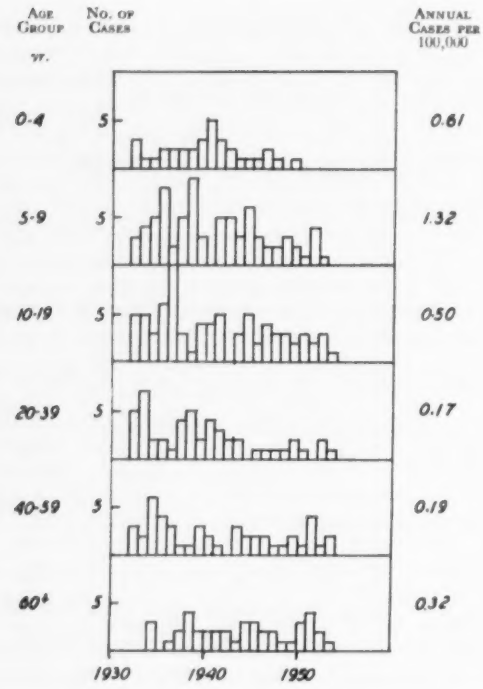

FIGURE 2. *Reported Cases of Tetanus, by Age Groups (Massachusetts, 1932-1953).*

previous decades to the last decade deaths decreased but slightly, and an ominous rise in adult case mortality was noted. The increase is understandable, if the very high fatality of about 50 per cent in patients over sixty years of age is remembered. Later years have shown a conspicuous number of diphtheria cases in old people.

The trends in age-specific mortality are shown in Figure 1. The same rate of decrease occurred in all age groups until about 1940, when the reduction either leveled off or, as in the age groups over forty, turned into an increase. Although the decrease in the children may be ascribed to immunization that in the adults was mainly due to an almost complete disappearance of the reservoir of disease in children. The same reservoir also served to maintain immunity in adults. Without this reservoir adult immunity is not stimulated, and diphtheria becomes mainly a problem of adults.

Tetanus

The reservoir of tetanus is in soil and excrement. Immunization will only benefit those who are immunized — the nonimmunized are exposed to risk of infection to the extent that they suffer from contaminated wounds. There are two immunized groups in Massachusetts at present: young children and adult men who have served in the armed forces.

TABLE 2. *Diphtheria Antitoxin in Adult Serum, by Age and Sex.*

	Age	Persons with Less Than 0.001 Antitoxin Unit	Persons with 0.001 −0.01 Antitoxin Unit	Persons with 0.01 −0.1 Antitoxin Unit	Persons with 0.1 −1.0 Antitoxin Unit	Persons with More Than 1.0 Antitoxin Unit	Totals	Percentages with Less Than 0.01 Antitoxin Unit
	yr.							
Men:								
	15-19	2	1	9	3	5	20	15.0
	20-29	24	13	12	12	6	67	55.2
	30-39	17	3	6	6	4	36	55.5
	40-49	6	1	2	3	3	15	46.7
	50-59	6	2	2	2	2	14	57.1
	Over 60	7	1	3	4	1	16	50.0
	Totals	62	21	34	30	21	168	
	Averages							49.4
Women:								
	15-19	7	0	6	7	2	22	31.8
	20-29	21	15	12	11	3	62	58.1
	30-39	19	8	11	5	2	45	60.0
	40-49	8	1	2	2	1	14	64.3
	50-59	8	3	2	2	0	15	73.3
	Over 60	5	2	6	2	0	15	46.7
	Totals	68	29	39	29	8	173	
	Averages							56.0

Although the disease is rare it is reported frequently enough for some information to be derived from a study of the prevalence over a number of years. Figure 2 gives the annual number of reported cases by age groups in the last twenty-two years. Similar data, in tabular form, have already appeared in the *Journal*.[8]

Antitoxin Levels in Adult Serum Samples

To estimate the present status of immunity among adults in Massachusetts, a series of antitoxin titrations in adult serum was performed during the spring

Table 3. *Tetanus Antitoxin in Adult Serum, by Age and Sex.*

	Age	Persons with Less Than 0.0025 Anti-toxin Unit	Persons with 0.0025 –0.025 Anti-toxin Unit	Persons with 0.025 –0.25 Anti-toxin Unit	Persons with 0.25 –2.5 Anti-toxin Unit	Persons with More Than 2.5 Anti-toxin Unit	Totals	Percentages with Less Than 0.0025 Antitoxin Unit
	yr.							
Men:								
	15-19	16	1	0	1	2	20	80.0
	20-29	29	2	5	17	15	68	42.6
	30-39	5	4	7	11	9	36	13.8
	40-49	4	3	4	2	2	15	26.6
	50-59	12	1	1	0	1	15	80.0
	Over 60	17	0	0	0	0	17	100.0
	Totals	83	11	17	31	29	171	
	Averages							48.5
Women:								
	15-19	18	0	1	0	1	20	90.0
	20-29	57	1	3	3	3	67	85.0
	30-39	36	2	3	3	1	45	80.0
	40-49	15	0	0	0	1	16	93.8
	50-59	14	0	0	0	1	15	93.3
	Over 60	15	0	0	0	0	15	100.0
	Totals	155	3	7	6	7	178	
	Averages							87.1

The annual incidence of tetanus over the last twenty-two years was 0.35 per 100,000. The highest frequency was in the group five to nine years of age (1.35 per 100,000) and in young children four years of age and younger (0.64 per 100,000).

There was a noteworthy decrease in the latter group, in which no cases have occurred in the four years since 1949. There was also some reduction in the number of cases among children five to nine years of age. The decrease among adults twenty to thirty-nine years of age in the early 1940's was referred to above but cases in people over forty years continue to occur with the same frequency as in earlier decades.

The trends permit the inference that the rate of decrease in each age group is proportional to the extent of tetanus immunization among persons of that age. With continued immunization of children tetanus will remain a disease of adults only, particularly of women and older people. Prophylactic tetanus serum injections will continue to exert some control, but it must always be kept in mind that half of the cases of tetanus arise with no conspicuous injury to indicate injection of serum.[9]

of 1954. Samples, sent to the Wassermann Laboratory of the Institute, were selected in representative numbers for each age group and sex, after completion of the serologic test for syphilis. A great majority of these samples were sent in for premarital tests. The antitoxin titrations on such serums have several advantages over Schick tests: they cause no extra inconvenience to the patients, they are more quantitative, and they offer a more nearly random selection of samples from a large population. Finally, for this purpose, information on tetanus immunity could be derived from the same sample. Actually, the economy of this procedure was increased by the performance of titrations for both antitoxins on the same day, the same tenfold dilutions of serum being used for both titrations.

Diphtheria antitoxin was measured by the rabbit intradermal method, testing for 0.001, 0.01, 0.1 and 1.0 unit. Tetanus-antitoxin titration was performed in mice, testing for 0.0025, 0.025, 0.25 and 2.5 units with 1 mouse for each dilution.

Tables 2 and 3 demonstrate the frequencies of titers at different ages, and in men and women. The sex groups differ greatly in immunity to tetanus (Fig. 3), as shown by the percentages of persons with no measurable antitoxin. The presence of tetanus antibody seems principally related to military service, as evidenced by a high immunity rate (87 per cent) of men between thirty and forty years of age. Few young adults have measurable antitoxin, and no more than 20 per cent of women thirty to forty years old have signs of active immunization. No persons over sixty years of age have any tetanus antitoxin.

No significant difference between sexes is found in diphtheria-antitoxin distribution. The age groups are

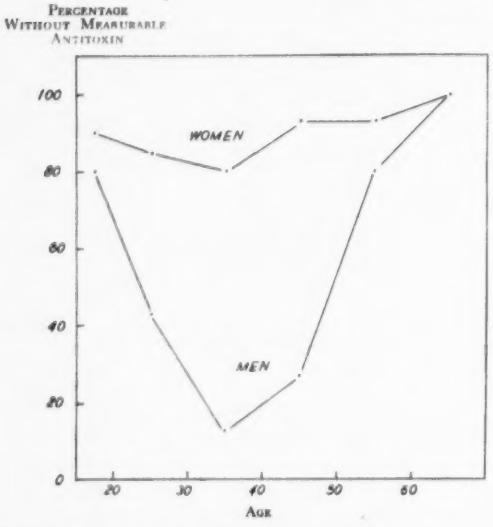

FIGURE 3. *Tetanus Immunity among Adults (Massachusetts, 1954).*

best compared in terms of percentage of persons having less than 0.01 diphtheria antitoxin unit — a level that corresponds roughly to the Schick-immunity threshold. Whereas only 24 per cent of persons fifteen to nineteen years of age were below that level, all age groups over twenty years of age contained about 55 per cent of persons with no "Schick" immunity.

Figure 4 presents a comparison of the diphtheria immunity of adult persons in Massachusetts in 1954 with similar data for adult persons in the city of Copenhagen, Denmark (population 700,000) in 1937 and 1944. Similar titrations on serum samples were conducted at that time.[10] The high percentage of nonimmunity in young adults fifteen to nineteen years of age is owing to the fact that no concerted diphtheria immunization was done in Copenhagen before child immunization became general in 1940. Between 1937 and 1944 the incidence of diphtheria was relatively low in Copenhagen, and a corresponding drop in immunity is noted. Nonimmune persons in 1944 were about 10 per cent above those in 1937 at all ages. Still, the status of the adult immunity in Copenhagen in 1944 was somewhat better than that in Massachusetts at present. The comparison is pertinent, because 1944 was the year when a serious diphtheria epidemic started in Copenhagen — an epidemic that in the next two years amounted to 2200 cases, of which 1500 were in adult persons. Thorough child immunization in the previous years afforded relative protection, so that adult cases exceeded child cases for the first time in the experience of the city.

The data are offered in evidence that the present immune status of the adults in Massachusetts does not ensure against future diphtheria epidemics.

REACTION AND RESPONSE IN ADULT DIPHTHERIA IMMUNIZATION

The diphtheria immunity of adults in Massachusetts is at a level where introduction of virulent strains of *Corynebacterium diphtheriae* could cause serious epidemics. Also, two thirds of the population are unprotected against tetanus. There is need for a toxoid mixture that can act as a booster immuniza-

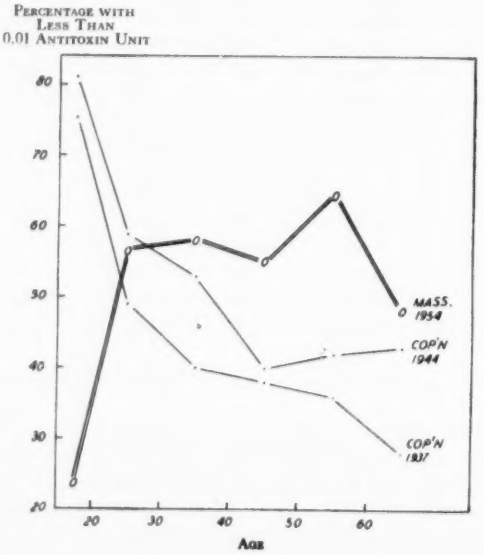

FIGURE 4. *Comparison of Diphtheria Immunity of Adults in Massachusetts (1954) and Copenhagen, Denmark (1937 and 1944).*

tion for diphtheria and as basic immunization against tetanus. Although tetanus immunization causes very little discomfort in any age groups the greatest objection to diphtheria vaccination of adults is the relatively high frequency of undesirable local and general reactions to diphtheria toxoid. There are several factors that influence the frequency: immunity status and previous exposure to *C. diphtheriae;* age; purity of toxoid; and dose of toxoid, in terms of antigen (L_f units).

It is well established that reactions in adults are most frequent among Schick-negative persons[8] and

among those who react to an intradermal injection of diluted toxoid (Schick control). Age frequency of reaction is not strictly correlated to immune status. Although reactions are seen more often in persons thirty to forty years of age than in those twenty to thirty years old[9] there seem to be considerably fewer reactions among people over fifty years of age, in spite of a similar proportion of immunity in those age groups.[6]

Purification of diphtheria toxoid may cause some decrease in reaction. Differences in reaction to crude and to purified toxoid were noted by Pappenheimer et al.[5] and James, Langshore and Hendry,[4] but the difference was clear only in young adults under thirty. High-purification (about 95 per cent) toxoid nitrogen did not accomplish notably lower reactivity than partial-purification (about 70 per cent) toxoid nitrogen. The role of alum adjuvants in reaction is not clear. There is no evident reduction in reaction to alum toxoids.

The importance of dosage is established in several field studies of adult population. Scheibel and her associates[6] used doses of purified toxoid of 25, 12.5 and 5 L_f in immune adults from fifteen to seventy-four years of age, with no reactions in 64, 71 and 78 per cent respectively. James, Langshore and Hendry[4] used 25 L_f and 5 L_f purified in high-school students, of whom 26 per cent were nonimmune (less than 0.004 unit). They found a similar occurrence of nonreactors, 65 and 78 per cent, respectively.

Severe reactions were similarly lower in both studies — 24 and 15 per cent in the former and 8 and 6 per cent in the latter study. What constitutes severe reaction is a matter of definition and not easily translated from one study to the other.

Of the four factors that influence reaction to diphtheria toxoid three are amenable to adjustment in the practice of immunizing adults.

Purification of the prophylactic to a certain degree seems a first step, but is not wholly satisfying.

Selection of subjects by previous intradermal testing with Schick toxin and toxoid is a cumbersome procedure and not always as profitable as one might hope. A positive Schick reaction is in itself an unpleasant reaction, at least as unpleasant as that experienced by most people to small doses of toxoid.

Reduction of the dose to a minimum effective level seems the most promising solution to the problem of booster immunization of adults. The difficulty is to find the optimum balance between effective response and untoward reaction.

Several workers find very little reaction in adults to doses of purified diphtheria toxoid (about 1 L_f) Edsall, Banton and Wheeler[2] noted that doses ranging from 1 L_f to as low as 0.008 L_f caused satisfactory rises in antibody titer in adult males with low antibody titers. However, 1 L_f gave a clearly superior response. Scheibel and Tulinius[7] reported that two doses of 1 L_f a month apart gave a very low antibody production in nonimmune adults, but a third dose a year later produced excellent antibody levels.

It has been recommended that 0.1 cc. of the Massachusetts diphtheria-tetanus toxoid be given to high-school students,[1] on the basis of the experience that a high proportion of Schick-positive persons become negative and very few have discomfort with that dose, which corresponds to 1.5 to 2.0 L_f of diphtheria toxoid.

The Commission on Immunization of the Armed Forces Epidemiological Board conducted trials with a combined diphtheria-tetanus toxoid that contains 1 L_f of diphtheria toxoid in 0.5 cc. Less than 5 per cent systemic reaction was observed among Air Force recruits.[11] On the basis of such studies this type of combined toxoid is recommended for universal use in the armed forces.

Diphtheria-Tetanus-Toxoid Combination for Adult Use

Following the proposal of the Armed Forces Epidemiological Board, the Biologic Laboratories are preparing a special combined diphtheria and tetanus toxoid for adult use.

The present product for use in children contains a diphtheria component too high to be recommended for adults even in doses of 0.1 cc., although this dosage can be given to children of high-school age. Doses smaller than 0.1 cc. cannot readily be administered, and the product would then not serve the purpose of conveying a basic tetanus immunity.

The new product, which will be available soon after release from the National Institutes of Health, will contain 1 L_f of diphtheria toxoid and 5 L_f of tetanus toxoid in a dose of 0.5 cc. The toxoids are purified — approximately 1600 L_f per milligram of nitrogen in the diphtheria toxoid and approximately 1000 L_f in the tetanus toxoid. No alum is added, so that the product has the appearance of a water-clear fluid.

Several field tests* have been carried out in adult populations with this product in comparison with the effect of a toxoid mixture that was alum precipitated but contained the same amount of antigen. The results are discussed below.

Persons Previously Immunized against Diphtheria and Tetanus

Eighty-seven young men, inmates of Wrentham State School, were divided into equal groups and given one injection, either alum-precipitated or fluid-combined toxoid. All had been immunized against diphtheria at least at the time of entry to the school. Thirty-six men had had two injections of tetanus toxoid a year previously.

Titers of both diphtheria and tetanus antitoxin rose promptly, and the effect was equally well induced by

*The trials were conducted under the sponsorship of the Commission on Immunization, Armed Forces Epidemiological Board, and were supported in part under contract with the Office of the Surgeon General, Department of the Army. Detailed data are available to interested readers on request.

the fluid and the alum-precipitated toxoid. Table 4 shows the dependence of the diphtheria response to the titer before the booster immunization. Curve A and

TABLE 4. *Diphtheria-Antitoxin Titer in Adult Men, before and One Week and Three Weeks after One Injection of 1 L, Diphtheria Toxoid*

Titer before Booster	Alum-Toxoid Antitoxin Titer			Fluid-Toxoid Antitoxin Titer		
	no.	at 1 wk.	at 3 wk.	no.	at 1 wk.	at 3 wk.
<0.001	1	0.10	3.2	0	—	—
0.001 – 0.01	3	0.32	2.1	4	0.10	1.3
0.01 – 0.1	8	0.56	4.2	8	0.49	10.0
0.1 – 1.0	19	0.84	4.8	25	1.9	11.0
>1.0	6	3.20	4.7	3	3.2	15.0
Totals	37			40		
Averages		0.84	4.3		1.06	9.0

G in Figure 5 are the responses to tetanus one and three weeks after the booster dose. The same response occurred whether 0.1 or 0.5 cc. was used as the booster dose of either toxoid.

Schick-Positive Persons

Medical students who were found to be Schick positive as a result of routine tests in the bacteriology course were given an injection of 0.5 cc. of either of the two toxoids. Four weeks later 29 (67 per cent) had more than 0.01 diphtheria antitoxin unit. The fluid toxoid showed, fortuitously, a somewhat higher response than the alum preparation (85 as against 52 per cent).

Primary Tetanus Response in Nonimmune Subjects

Fifty men from Wrentham State School had no previous tetanus experience. The response after one dose is shown in Table 5. There was a striking difference in response according to size of dose, but only a slight effect with the alum adjuvant. The effect was more pronounced after twenty-eight weeks, and

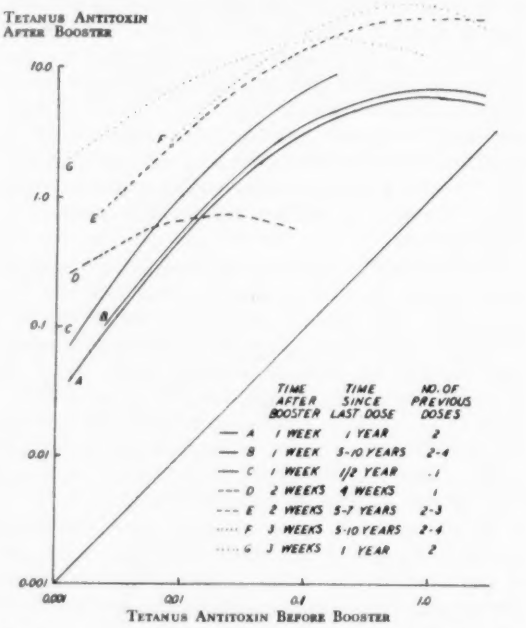

FIGURE 5. *Responses to Tetanus One to Three Weeks after a Booster Dose.*

two toxoids had been compared in their ability to produce tetanus immunity in mice and in guinea pigs. In mice about thirty times more fluid toxoid than alum toxoid was required to induce 50 per cent immunity to challenge with toxin. Antibody production in guinea pigs gave an estimate of about a hundredfold difference in potency.

These experiments again emphasize the great caution required in the application of quantitative data from animal experiments to circumstances in man. Much of the claim to superiority of alum toxoids is derived from experience in animal experiments.

TABLE 5. *Tetanus-Antitoxin Titer in Adult Men with No Previous Tetanus Immunization.*

Toxoid*	Dose of Toxoid	No. of Persons	Mean Antitoxin Titer			
			1 wk. after 1st dose	3 wk. after 1st dose	28 wk. after 1st dose	1 wk. after second dose†
	L/					*antitoxin units*
Alum	1	17	None	0.0038	0.0038	0.25
	5	8	None	0.013	0.017	3.5
Fluid	1	14	None	0.0028	0.0018	0.044
	5	11	None	0.027	0.0045	0.46

*Combined diphtheria & tetanus toxoid for adult use.
†Each group received all 4 primary treatments as 2d dose.

indicated a fourfold difference in the ability of the two preparations to confer basic immunity.

This difference, however, was much smaller than that anticipated from animal experiments. The same

Reactions

The experience with untoward reactions of the new products concurs with that in the trials in the armed forces. No noteworthy reaction was observed among

the inmates of the Wrentham State School. Only 2 of 43 medical students complained of general reaction that lasted more than 24 hours.

To summarize these observations, the product was found highly satisfactory as a secondary — or booster — stimulus for diphtheria and tetanus immunity; two injections induced ample basic tetanus immunity, and the preparation was well tolerated in adults between twenty and forty years of age.

Recommendation for Use in Adults

It is not my purpose to advocate mass immunization of adults as a short-term project. The aim is to place at the disposal of the medical profession a means of continuing the excellent program for childhood immunization into adulthood. For diphtheria the intent is to imitate a task formerly performed by nature — that of maintaining diphtheria immunity by a slow, trickling stimulus. For tetanus there is both the problem of giving basic immunity to those who have not yet had it and that of maintaining the immunity.

The reason for recommending a fluid diphtheria-tetanus preparation for adult use is that the water-clear fluid is readily distinguished from the turbid alum-precipitated preparation intended for children. The evidence brought out in the foregoing section indicates that the fluid preparation is comparable in effect to the alum precipitated. If the child preparation is given by mistake to adults, unpleasant reactions may occur.

How frequent is it necessary to repeat toxoid injections? Experience that is gained from study of persons who received basic immunity some years previously indicates that ability to react promptly to booster injection is maintained for at least ten years.[5,6] In fact, one can do more harm by shortening the periods of injection than by prolonging the intervals between booster doses. Much "telescoping" of injection schedules is done in the face of emergency or for the convenience of patients and physicians. In a program of maintaining immunity it is more important to spread booster injections over the life span of the adult person than to try to concentrate many injections over a short interval.

Figure 5 demonstrates antibody response when booster doses of tetanus toxoid are given at various times after primary immunization. The response is measured one week (A, B and C), two weeks (D and E) and three weeks (F and G) after the booster injection. Intervals of half a year to ten years make no significant difference in the degree of response. Only one set of data (Curve D) falls outside the general trend. In this instance, the second injection was given four weeks after the first. The response is particularly lower in persons with relatively high antibody titers.

My recommendations for the use of the combined products are as follows (in all cases the dose recommended is 0.5 cc.):

General use. Each physician is advised to keep a stock of the product in his office refrigerator and to induce his adult patients to have an injection once every five to ten years. It is not necessary to perform a Schick test to select persons with low diphtheria immunity. Such a procedure would only complicate the matter and increase the visits and work.

Persons with no previous tetanus immunity. Two injections are recommended, not less than six weeks apart. No harm is done if the second dose is postponed for several months. A third injection may be given a year later, but again this interval can be stretched for convenience.

Tetanus prevention in wounded and other surgical cases. As a general rule tetanus toxoid should always be injected in cases of injury and major surgical operations. Tetanus antitoxin should be given simultaneously in all cases in which there is doubt about previous effective toxoid immunization. Persons who under these circumstances receive toxoid for the first time should be followed through a full course of immunization as outlined above. (The new product can be substituted advantageously for the fluid tetanus toxoid, which was formerly recommended in these cases; the fluid toxoid is not purified.)

Exposure to diphtheria. A case of clinical diphtheria in the neighborhood should always serve as motivation for booster injection of toxoid of both children and adults.

Travel. Tetanus and diphtheria immunization are usually not compulsory for entering foreign countries or re-entry to the United States. There are, however, reasons to advise diphtheria booster immunization before travel to most countries, and the occasion is, in all cases, opportune to suggest tetanus and diphtheria toxoids, combined, for adult use, as the immunization of choice.

Summary

A tetanus-diphtheria toxoid preparation containing 1 L_f of diphtheria toxoid and 5 L_f of tetanus toxoid, purified, without alum adjuvant, is recommended for adult use in the civil population. Diphtheria experience in Massachusetts in later years shows a prevalence of adult cases. Tetanus cases have decreased only in children and Army veterans. Samples of adult serum demonstrate that 55 per cent of all persons over twenty years have less than 0.01 unit of diphtheria antitoxin.

The preparation is recommended for routine use in adult persons with an interval of five to ten years and at times of exposure to either disease.

I am indebted to Miss Genevieve Stuart, senior bacteriologist, Wassermann Laboratory, and to Mrs. Hanna Sylwestrowicz, who performed the antitoxin titrations. Dr. Wiggin L. Merrill, Wrentham State School, gave excellent help in the field study, and Dr. Harry E. Bowen organized the study at Harvard Medical School.

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PREVENTION OF RHEUMATIC FEVER BY TREATMENT OF PREVIOUS STREPTOCOCCAL INFECTIONS*

I. Evaluation of Benzathine Penicillin G

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RHEUMATIC fever can be prevented by adequate treatment of the preceding streptococcal respiratory infection.[1,2] Most therapeutic regimens thus far recommended require either frequent oral medication for at least a week or multiple parenteral injections. A disadvantage of oral therapy is that it places the responsibility of maintaining treatment on the patient. In the majority of cases the symptoms of the streptococcal infection subside within three to five days, and the patient may then haphazardly take the medication or discontinue it completely. The physician can ensure adequate therapy for the prevention of rheumatic fever by the parenteral administration of penicillin. Since multiple injections have been required this procedure has not been widely employed in clinical practice.

An ideal method for the treatment of streptococcal infections for the prevention of rheumatic fever would employ a single injection of drug that the physician could administer to the patient at the time the diagnosis is made. The introduction of dibenzylethylenediamine (DBED) dipenicillin G,‖ a depot preparation that is slowly absorbed over a period of at least ten days,[3] presented the opportunity to determine whether a single injection of this compound would prevent rheumatic fever.

Before a large-scale investigation of DBED penicillin was instituted it was desirable to obtain information concerning the amounts to employ and the relative effectiveness of this preparation as compared to that of previously established methods of treatment. Since elimination of the infecting streptococcus from the oropharynx of patients with streptococcal pharyngitis is an essential factor in the prevention of rheumatic fever[4] one can readily ascertain the antirheumatic effect of a drug by determining the ability of therapy to eradicate these organisms.

This is a report of a preliminary evaluation of two different doses of DBED penicillin in the treatment of streptococcal pharyngitis. The results indicate that this compound may prove to be extremely valuable in the treatment of these infections and in the prevention of rheumatic fever.

Selection of Patients and Methods

Airmen admitted to the Warren Air Force Base Hospital with respiratory disease were examined within a few hours by a member of the professional staff of the laboratory. Patients who exhibited exudative tonsillitis or pharyngitis were included in the study except for those who had had a previous attack of rheumatic fever, previous allergic reaction to penicillin or a suppurative complication at the time of admission.

Each patient was examined twenty-one days after the onset of illness. Patients in the control group who remained at Warren Air Force Base were again examined at thirty-five days whereas those who had received treatment were studied at weekly intervals for seven weeks. At each follow-up examination symptoms of pain or swelling of the joints, feverish-

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‖Kindly supplied as Bicillin by Dr. Edward F. Roberts, of Wyeth, Incorporated, Philadelphia.

ness, skin rash or sore throat were recorded. Persons with signs or symptoms of rheumatic fever were hospitalized on a special study ward. The diagnosis of acute rheumatic fever was made according to a modification[5] of the classification of Jones.[6]

Laboratory procedures at the time of acute infection, follow-up examinations and hospitalization for suspected rheumatic fever were performed in a standard manner. Cultures of the oropharynx were obtained by the physician and within an hour were streaked on sheep blood-agar plates. Beta-hemolytic streptococci were identified serologically according to the method of Swift, Wilson and Lancefield.[7] A modification of the technic of Hodge and Swift[8] was employed for the determination of antistreptolysin "O" titers on acute-phase and convalescent-phase serums.

The therapy each patient received during the first portion of the study (Schedule I) was determined by Air Force serial number and so arranged that more patients were placed in the penicillin-treated group than in the controls (Table 1). DBED penicillin was administered in a dose of 1,200,000 units to 132 men, of whom 92 received a single intramuscular injection, and 40 received two simultaneous injections of 600,000 units each. Placebo injections were administered to the control patients.

In contrast to Schedule I all patients in Schedule II received therapy (Table 1). A dose of 600,000 units was given intramuscularly to patients with exudative tonsillitis or pharyngitis who were to remain at the military base three or four weeks except for a week in April when all such patients were treated. During this schedule patients who gave a family history of rheumatic fever were excluded from the study.

TABLE 1. *Distribution of Cases of Exudative Pharyngitis and Tonsillitis According to Treatment.*

DIBENZYLETHYLENEDIAMINE (DBED) DIPENICILLIN G	INCLUSIVE DATES OF STUDY	NO. OF PATIENTS	
		PENICILLIN	PLACEBO
Schedule I—1,200,000 units			
Administered intramuscularly as:			
Two simultaneous injections of 600,000 units	Jan. 4, 1953-Jan. 18, 1953	40	30
Single injection	Jan. 19, 1953-Feb. 18, 1953	92	79
Schedule II—600,000 units			
Administered as single intramuscular injection	Mar. 16, 1953-July 9, 1953	125	—
Totals		257	109

Most of the infections observed were streptococcal in origin, as indicated by the isolation of Group A streptococci from the oropharynx and the demonstration of a leukocytosis in most cases (Table 2). A diagnostic increase in antistreptolysin titer was demonstrated in the serums from approximately 80 per cent of the patients in the placebo group. During the period when 1,200,000 units of DBED penicillin was administered (Schedule I) the treated and placebo groups were comparable except for a somewhat different distribution of serologic types of streptococci. During both treatment schedules therapy was instituted in 90 per cent of the patients before the fourth day of illness.

TABLE 2. *Comparability of Patients in Study Groups.*

STUDY GROUP	TREATMENT SCHEDULE I		TREATMENT SCHEDULE II
	DBED PENICILLIN (129 PATIENTS)*	PLACEBO (89 PATIENTS)	DBED PENICILLIN (119 PATIENTS)
	%	%	%
Group A streptococci on initial throat culture	82	82	94
Type distribution of Group A streptococci:			
Type 3	17	10	22
Type 12	5	7	1
Type 14	4	0	22
Type 19	27	47	24
Type 30	29	26	23
Nontypable	6	4	1
Other	12	6	7
Initial antistreptolysin "O" titer 125 units or less	72	72	83
Duration of illness to time of treatment:			
1-23 hr.	38	37	36
24-47 hr.	38	46	48
48-71 hr.	14	7	14
72 hr. & over	10	10	2
White-cell count:			
10,000 or more	80	81	78
12,000 or more	67	62	65
Family history of rheumatic fever	9	9	0
Scarlet fever	2	1	2

*Patients excluded from this analysis & subsequent bacteriologic and serologic analyses were as follows: from placebo group and DBED-penicillin-treated groups in Schedules I & II suppurative complications developed in 13, 2 & 2 patients respectively; from placebo group & DBED penicillin-treated groups in Schedules I & II there were 6, 0 & 3 patients, respectively, who inadvertently received other than prescribed treatment. Three patients, 1 from each group, who had exudative pharyngitis & concomitant rheumatic fever were also excluded; no acute rheumatic fever developed in other excluded patients.

RESULTS

The effect of treatment with DBED penicillin on the Group A streptococcus responsible for the observed attack of exudative tonsillitis or pharyngitis is shown in Table 3. The infecting type of streptococcus was isolated twenty-one days after the onset of illness from only 1 patient who received penicillin. In contrast the infecting organism was isolated from 80 per cent of the control patients at this time. Thirty-five days after onset of the acute illness the infecting type of streptococcus was isolated from a patient who received 1,200,000 units and from 4 who received 600,000 units. Cultures were obtained forty-nine days after illness from 28 and 47 patients who received 1,200,000 and 600,000 units of DBED penicillin respectively, and only 1 additional patient in the former group showed the infecting organism. These studies demonstrate that elimination of the infecting organism by both 1,200,000 and 600,000 units of DBED penicillin was essentially complete as determined by

the follow-up culture on the twenty-first day. However, additional cultures obtained thirty-five days after onset showed that 5 of 115 patients who received

TABLE 3. *Bacteriologic Results as Determined at the Convalescent Examinations.*

Day of Convalescent Examination According To Type of Treatment	Patients with Typable Group A Streptococci Isolated from Admission Culture	Follow-up Cultures Compared To Admission Cultures		
		No. of same type	No. of new type	No. non-typable
Schedule I (1,200,000 units):				
21st day	93	1	0	0
35th day	45	1	0	0
Total patients	93	1	0	0
Placebo				
21st day	66	53	1	2
35th day	58	34	9	5
Total patients	67	58	10	7
Schedule II (600,000 units):				
21st day	102	0	3	1
35th day	70	4	4*	1
Total patients	104	4	5	2

*In addition to regular culture swabs processed in Pike's[9] selective medium, 8 streptococci of new type isolated from 2 additional patients not recorded.

treatment harbored the infecting type of streptococcus.

Penicillin appeared to be active longer in the patients receiving 1,200,000 units than in those given 600,000 units. New serologic types of streptococci were isolated from 5 patients in Schedule II by the thirty-fifth day, whereas 10 of the control patients had acquired new organisms by this time. No acquisitions of streptococci were identified in patients who received 1,200,000 units of DBED penicillin. The first recurrent streptococcal infection occurred forty-seven days after treatment in Schedule I as compared to thirty-six days in Schedule II (Table 4). However, it cannot be stated with certainty that patients in Schedule I were protected against reinfection for forty-seven days since only 2 infections were observed in the placebo group before this time. It is apparent from Table 4 that patients in Schedule I were no longer protected against new streptococcal illnesses seven weeks after treatment. The occurrence of only 1 recurrent streptococcal illness in Schedule II may be explained by the fact that this portion of the study extended into the summer months, when the incidence of streptococcal infections was low.

TABLE 5. *Influence of Dibenzylethylenediamine Dipenicillin G on Antistreptolysin "O" Production in Patients with Acute Streptococcal Pharyngitis.**

Phase	Schedule I		Schedule II
	Average titer on 1,200,000 units of DBED penicillin (94 patients)	Average titer on placebo (64 patients)	Average titer on 600,000 units of DBED penicillin (98 patients)
	units	*units*	*units*
Acute	124	126	114
3 wk. convalescent	172	374	156
Average unit rise	48	248	42

*Includes only patients from whom Group A streptococci isolated on admission.

The effect of DBED penicillin on the serologic response of the patients to the infection is presented in Table 5. Only subjects from whom Group A streptococci were isolated from the initial oropharyngeal culture were considered in this analysis. The average increase in antistreptolysin titer in the convalescent-phase serums of the groups treated with penicillin was 48 and 42 units for Schedules I and II, respectively, in contrast to an average increase of 248 units for the control group. This represents 81 per cent inhibi-

TABLE 4. *Comparison of the Time of Development of a Second Attack of Exudative Tonsillitis or Pharyngitis according to Treatment.*

DBED Penicillin (132 Patients) on Schedule I			Placebo (109 Patients) on Schedule I*			DBED Penicillin (125 Patients) on Schedule II		
Interval between illnesses	Type of streptococcus		Interval between illnesses	Type of streptococcus		Interval between illnesses	Type of streptococcus	
days	*1st illness*	*2d illness*	*days*	*1st illness*	*2d illness*	*days*	*1st illness*	*2d illness*
47	19	30	6	30	19	36	18	24
52	19	30	34	18	30			
55	3	14	52	30	3			
56	19	18	59	18	30			
57	12	19	79	30	19			
60	19	14						
87	19	30						
97	3	14						

*Two patients readmitted on 7th day after onset of illness with same type of streptococcus as recovered during original infection.

tion of antistreptolysin formation by the administration of 1,200,000 units. No appreciable increase in formation of antibody was detected in the thirty-fifth-day and forty-ninth-day convalescent-phase serums of the treated patients, indicating that the result of DBED penicillin was not merely to delay the appearance of antibody.

The effect of therapy on the occurrence of complications is shown in Table 6. From the control group there were 11 patients in whom a suppurative complication developed twenty-four hours or more after admission. Roentgenologic evidence of pneumonitis was demonstrated in 5 patients. The occurrence of an influenzal epidemic during the first weeks

TABLE 6. *Complications Occurring after the First Twenty-Four Hours of Treatment.*

COMPLICATION	SCHEDULE I		SCHEDULE II
	NO. ON DOSAGE OF 1,200,000 UNITS OF DBED PENICILLIN (132 PATIENTS)	NO. ON PLACEBO (109 PATIENTS)	NO. ON 600,000 UNITS OF DBED PENICILLIN (125 PATIENTS)
Sinusitis	1	3	0
Otitis media	0	1	0
Peritonsillar cellulitis	0	1	0
Cervical adenitis	0	1	0
Pneumonia	0	5	0
Acute glomerulonephritis	0	1	0
Definite rheumatic fever	0	2	0
Possible rheumatic fever or penicillin reaction	5	0	1
Monarthritis or monarthralgia	1	0	3
Skin rash	2	1	1

of this investigation may have been partially responsible for this complication. In 3 of the patients with pneumonia from whom paired serums were available for study a diagnostic increase in antibodies against influenza A′ was demonstrated. Only 1 patient who received penicillin manifested a suppurative complication. This patient had symptoms and signs of sinusitis, which required surgical drainage ten days after the administration of 1,200,000 units of DBED penicillin.

In 1 patient from the placebo group acute glomerulonephritis developed seventeen days after onset of a Type 12 streptococcal infection. Two examples of classic acute rheumatic fever were observed in the control group twenty-seven and thirty-six days after the onset of the streptococcal pharyngitis. Type 18 streptococcus was isolated from the oropharynx at the time of onset of both illnesses in the former patient, whereas in the latter, Types 19 and 30 streptococci were isolated at the admissions for respiratory and rheumatic disease, respectively. Definite nonsuppurative sequelae were not observed in the patients who received penicillin.

There were 10 patients who had one or more symptoms or signs frequently associated with rheumatic fever, but all these occurred in persons who had received treatment (Table 6). Because of the clinical similarity between the manifestations of mild acute rheumatic fever and reactions to penicillin it was not possible to state unequivocally whether these abnormalities represented a poststreptococcal complication or a penicillin reaction. Details of these cases are presented below.

Three patients who had received 1,200,000 units of DBED penicillin (Schedule I) exhibited polyarthritis, fever and urticaria, and these manifestations were considered to represent classic penicillin reactions. Another patient in Schedule I had polyarthritis and a pruritic maculopapular skin eruption. Cardiac examinations were negative, and repeated electrocardiograms were normal. No fever was recorded. The sedimentation rate was not increased nor was C-reactive protein detected in the serums. Cultures of the throat, positive for Group A streptococci during the respiratory illness, were repeatedly negative thereafter. The serum antistreptolysin titer was initially less than 50 units and did not increase. The final diagnosis was a penicillin reaction. The other 2 patients listed as possible rheumatic fever or penicillin reactions (1 each from Schedule I and Schedule II) showed polyarthralgia, and, in addition, 1 showed monarthritis. At the time of onset of exudative pharyngitis no streptococcus was isolated, and the antistreptolysin titer in both cases was less than 50 units. Convalescent increases in antibody titer were not demonstrated. The patients were afebrile, and the sedimentation rates were normal. The patient in Schedule II (600,000 units), however, showed a PR interval of 0.21 second on one electrocardiogram.

There were 1 patient from Schedule I and 3 from Schedule II whose signs or symptoms were limited to one joint. Of the 3 from Schedule II 1 also had a pruritic, maculopapular rash, 1 had a low-grade fever, and the third had an elevated sedimentation rate. In these patients the abnormalities were insufficient for us to make a diagnosis of rheumatic fever or penicillin reaction.

In addition to the 10 patients discussed above, there were 4 in whom skin eruptions developed. One patient from the control group and 2 who received 1,200,000 units of penicillin manifested a pruritic skin eruption. One patient who received the smaller dose of DBED penicillin had urticaria as an isolated finding.

In summary, 4 of the 6 illnesses classified in Table 6 as possible rheumatic fever or penicillin reaction were associated with urticaria or pruritic skin eruptions. The other 2 patients had respiratory illnesses that were probably not due to the streptococcus. These data suggest that the 6 illnesses were complications of therapy with penicillin rather than nonsuppurative

complications of a streptococcal infection. The data obtained from the 4 patients whose signs or symptoms were limited to one joint were insufficient to establish a diagnosis of penicillin reaction, rheumatic fever or some other unrelated illness.

Pain at the site of the intramuscular injection of DBED penicillin was more intense and prolonged than that produced by other preparations of depot penicillin. About three fourths of the patients complained of discomfort, which lasted twenty-four to forty-eight hours, at the site of injection. The administration of the smaller dose of 600,000 units or division of the larger dose into two equal injections appeared to make little difference in the degree of discomfort. No sterile abscesses were observed.

Discussion

There is a need for a simple technic to determine the antirheumatic effect of antibiotics employed in the treatment of streptococcal infections. Today, many drugs are recommended as being useful in the therapy of such infections, but few or no data are available concerning their ability to prevent rheumatic fever and nephritis. Previously, it was necessary to treat large numbers of patients with streptococcal infections before a conclusion concerning the possible antirheumatic and antinephritic effects could be reached since the attack rate of these complications is low.

The method employed in the present study for the preliminary evaluation of DBED penicillin may prove useful in the investigation of other compounds. It is based on an analysis of over 3500 streptococcal infections treated with a variety of compounds showing that eradication of the infecting streptococcus is an essential factor in the prevention of rheumatic fever.[4,8,10] Treatment regimens that eliminate the organism should prove useful in the prevention of rheumatic fever and subsequent heart disease. Final evaluation can then be accomplished by the treatment of large numbers of proved streptococcal infections.

The method for testing the antirheumatic effect of new drugs should be based on careful bacteriologic and serologic studies of each patient at the time of the acute respiratory illness and at subsequent convalescent examinations. In such investigations the diagnosis of the streptococcal illness should be made from both clinical and laboratory data. Furthermore, the accuracy of the technics employed in the bacteriologic study of the patients during the acute illness and the subsequent follow-up examinations become extremely important. Under optimal conditions the infecting type of streptococcus can be isolated from all untreated patients for at least two months after infection.[4] The determination of the antistreptolysin response is a valuable check on the accuracy of the bacteriologic results. Since a rise in antistreptolysin titer during the convalescent period depends on the presence of the streptococcus, eradication of the infecting organism is accompanied by a striking suppression of the antibody response.

In the present study the technics employed were sufficiently accurate so that 80 per cent of the control group were found to harbor the infecting type as determined by a single culture obtained twenty-one days after the onset of illness. With the same methods 1 of 195 cultures was positive for the infecting type three weeks after treatment with DBED penicillin. At thirty-five days 4 other persons, all of whom had received 600,000 units, showed the infecting type. Cultures were obtained forty-nine days after onset of illness from 75 patients who received treatment, and the infecting type was isolated from only 1 additional person.

The most successful treatment of acute streptococcal illnesses for preventing rheumatic fever previously employed was a total of 1,200,000 units of procaine penicillin G containing 2 per cent aluminum monostearate divided into 3 injections given every other day.[5] Here the infecting type was isolated from 8 per cent of the treated group and from only 35 per cent of the controls three or four weeks after infection, indicating that the bacteriologic technics were not optimal. It thus appears that a single injection of DBED penicillin eliminated streptococci more effectively than 3 injections of the procaine preparation. The fact that there was an 81 per cent reduction in antibody formation in the group receiving 1,200,000 units of DBED penicillin, as compared to 51 per cent inhibition effected by the 3 injections of the depot penicillin,[5] confirms the impression that DBED penicillin more effectively eliminated streptococci. Since eradication of the streptococcus is important in the prevention of rheumatic fever[4] DBED penicillin administered in a single injection appears to be theoretically superior to other forms of therapy for streptococcal infections.

In the small group of patients studied 2 definite cases of acute rheumatic fever and 1 of acute nephritis developed in the control patients, whereas these complications did not occur among the patients who received DBED penicillin. In 6 of the treated patients illnesses characterized by multiple joint symptoms or signs appeared. Urticaria was present in 3, and a pruritic eruption in 1 of these patients. A fourth patient exhibited a prolonged PR interval on one electrocardiogram. These manifestations (dermatitis and prolonged PR interval) are observed in patients with penicillin reactions[4] whereas urticaria and pruritic eruptions are uncommon in the rheumatic patient. There is some evidence that reactions to penicillin are more likely to develop in patients receiving large doses of DBED penicillin,[11] and in the present study 5 of the 6 persons classified in Table 6 as having possible rheumatic fever or penicillin reaction had received the larger dose. It is apparent, therefore, that further data are required concerning the toxicity of DBED penicillin before the proper

dosage for the treatment of streptococcal infections can be determined.

The conclusion that DBED penicillin in a single injection will prevent rheumatic fever is supported by the studies of Breese,[12] who administered 600,000 units of DBED penicillin to 700 children with streptococcal infections without the occurrence of acute rheumatic fever. Until the frequency of reactions after large doses of DBED penicillin is established 600,000 or possibly 900,000 units of DBED penicillin intramuscularly is recommended for the treatment of streptococcal infections.

SUMMARY

A method for the evaluation of drugs in the prevention of rheumatic fever by the treatment of acute streptococcal illnesses is presented. A single intramuscular injection of dibenzylethylenediamine (DBED) dipenicillin G was administered to 257 patients with exudative pharyngitis whereas 109 patients served as controls. Eradication of the infecting organism was effected in 99 per cent of the treated group as determined by cultures of the throat twenty-one days after illness. In addition, there was striking inhibition of antistreptolysin formation. Definite nonsuppurative sequelae developed in 3 of the control patients whereas no such complications were observed in those who received therapy.

Available data indicate that DBED penicillin, in the doses recommended, should prove to be a highly effective agent in the prevention of rheumatic fever by treatment of the preceding streptococcal illness.

In most patients the administration of the DBED penicillin caused local discomfort at the site of injection. Symptoms and signs of reactions to penicillin developed in 8 patients receiving 1,200,000 units and 5 patients receiving 600,000 units of DBED penicillin.

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INTESTINAL PROTOZOA OF AMERICAN TRAVELERS RETURNING FROM EUROPE*

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EXPERIENCED travelers recall trips abroad that were memorable mainly for bouts of diarrhea. Few who have visited the Continent, Mexico or more distant lands are unacquainted with intestinal disease either from personal experience or from the tales of their companions. After the war, when millions of soldiers who had had diarrhea returned to the United States, there were dire predictions that a major increase in amebiasis and other intestinal infections might affect the civilian population. Sufficient time has elapsed to indicate that no major increase in intestinal infections derived from troops stationed abroad has occurred in this country.[1,2]

An interesting postwar phenomenon has been the growth of foreign travel. According to statistics released by the State Department at least 350,000 Americans visited Western Europe in 1953, and since World War II almost 1,500,000 Americans have visited continental Europe; most have gone to England, France, Germany and Italy.[3]

On theoretical grounds there are three likely causes of the diarrhea of travelers: food poisoning, especially by staphylococcal toxins; bacterial infections such as salmonellosis and shigellosis; and amebiasis and other protozoan infections. Little scientific support is available for the views that "water," "change in the diet" or "viruses" are causes of the diarrhea.

The occurrence of diarrhea shortly after arrival in a foreign country, a history of exposure to unusual or exotic foods and an explosive onset of symptoms, with many watery bowel movements, nausea, vomiting, some fever, severe exhaustion and rapid recovery, sug-

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gest the diagnosis of staphylococcal toxemia. Although the diarrhea produced by food poisoning may be extremely upsetting to the individual patient no public-health hazard is introduced to the country upon the return of the affected traveler.

The acute bacterial infections are much more important and may be responsible for later chronic disease.[4] As a rule, however, shigellosis and salmonellosis cause febrile illnesses of greater severity and longer duration than the typical enteritis of tourists. Only rarely do the pathogens persist in the stool.

The clinical picture of amebiasis may range from vague intestinal discomfort to typical bloody dysentery. Amebiasis, because of the public-health aspects of the disease, the potential seriousness of the infection to the patient and its protean manifestations, represents a major problem.

For these reasons an investigation was undertaken, to determine how much amebiasis was acquired by tourists in Europe. It was believed that protozoal infection might also be used as an index of the fecal contamination of water and food. If sufficient evidence of such a fecal contamination could be obtained, more complicated bacteriologic studies might be justified at a later date.

Method

Stools were obtained from students who visited Europe during the summer of 1953. The Council on Student Travel, which co-operated in this study, sponsors European travel for American students enrolled in colleges in the United States and Canada. In 1953 there were two sailings. The *Skaubryn* sailed from Montreal for Southampton and Le Havre on June 24, and the *Arosa Kulm* from Quebec on July 4. Although the ships sailed from Canadian ports for reasons of economy and expedience almost all the students were American. The return voyages were on the *Anna Salen,* which sailed on August 24 from Le Havre for New York, and the *Arosa Kulm,* which sailed on September 4 from Le Havre for Quebec. A third sailing on September 30 from Le Havre to Quebec was not included in the study. Seven hundred and forty-three students sailed on the *Skaubryn,* and 563 on the *Arosa Kulm;* 972 returned on the *Anna Salen,* and 773 on the *Arosa Kulm.*

Cardboard containers were placed in each of several toilets aboard ship. At half-hour intervals these were collected and taken to a central laboratory, where approximately 0.5 to 1.0 gm. of feces was introduced into a glass bottle containing freshly prepared MIF (merthiolate-iodine-formaldehyde) preservative stain; after thorough stirring the bottle was capped and labeled. This phase of the work was in charge of two medical students.

The MIF preservative stain was described by Sapero and his associates[5,6] after extensive trials in Egypt by United States Naval Medical Research Unit No. 3. It consists of merthiolate, iodine, formaldehyde and glycerin. In the preparation of our solutions the directions of these authors were carefully followed, the iodine being added to the merthiolate-formaldehyde solution shortly before the stool specimen was introduced.

On the voyages to Europe a total of 402 persons provided specimens. On the return trip 412 specimens were obtained. Of these 222 could be paired with specimens obtained from the same persons en route to Europe. Of the remaining 190 specimens, 10 were discarded by lot, leaving 180 from returning travelers to be compared with those of 180 different persons going to Europe.

Table 1. *Countries Visited by 402 Returning Travelers Whose Stools Were Examined.*

Country	No. of Students
France	335
Germany	266
England	218
Italy	181
Switzerland	175
Holland	149
Belgium	124
Austria	101
Denmark	63
Sweden	42
Spain	36
Norway	32
Scotland	31
Ireland	19
Yugoslavia	16
Luxembourg	10
Finland	8
Israel	5
Morocco	4
Portugal	3
Africa, Greece & Wales	2
Tangiers, Syria, Lebanon, Egypt, Algeria & Turkey	1

The 804 specimens were all examined by an experienced technician in the Parasitology Department of the Central Laboratories of the New York Hospital between September, 1953, and April, 1954. Representative portions of each fecal specimen were examined microscopically for an average of fifteen to twenty minutes. No concentration methods were employed since these have not been properly evaluated with the MIF technic.

The protozoa were easily visualized, but species identification was often difficult. Nuclei stained erratically. In some specimens the nuclear detail and chromatoidal bodies were remarkably well outlined; in others the cellular contents were blurred, and careful and prolonged study was necessary for identification. Trophozoites were often surprisingly well pre-

served although in some specimens they could be recognized only after considerable experience with the method had been acquired. On the whole we considered the MIF a satisfactory preservative stain and one that met the technical obligations of our study.

TABLE 2. *Parasites in Single Stool Specimens.**

ORGANISM FOUND ON ANALYSIS	PAIRED GROUP*		NONPAIRED GROUP†		TOTAL‡	
	STUDENTS GOING	STUDENTS RETURNING	STUDENTS GOING	STUDENTS RETURNING	STUDENTS GOING	STUDENTS RETURNING
Endamoeba histolytica	6	9	5	5	11	14
Probable *E. histolytica*	2	3	4	5	6	8
E. coli	17	22	13	21	30	43
Endolimax nana	25	30	22	24	47	54
Dientamoeba fragilis	7	4	8	8	15	12
Iodamoeba butschlii	5	4	2	5	7	9
Giardia lamblia	2	6	4	6	6	12
Chilomastix mesnili	0	0	2	1	2	1
Unidentified protozoa	1	1	1	1	2	2
One parasite	35	43	28	45	63	88
Two parasites	14	17	11	13	25	30
Three or more parasites	1	1	3	2	4	3
One or more parasites	50	61	42	60	92	121
Blastocystis hominis	51	52	55	56	106	108
Leukocytes	1	3	0	1	1	4

*Consisted of 222 students who provided specimens both going & returning.
†Consisted of 360 students, of whom 180 provided specimens on the trip over & 180 on the trip back.
‡Total specimens examined, 804.

RESULTS

The countries visited by the students are listed in Table 1. The results of the microscopical analyses of the 804 specimens are recorded in Table 2.

The advantage of having available for analysis a "paired group" is that this permitted determination of the number of individual acquisitions of parasites. Table 3 presents the results of the examinations on the return trip of the students whose stools had been positive on the way over. Table 4 shows the results of the examinations on the departure of students whose stools were positive on the return trip. (Tables 3 and 4 deal only with those 222 students who provided specimens on both trips.)

TABLE 3. *Results of Examinations on Return Trip of Students (Paired Group) Whose Stools Were Positive on the Trip over.*

ORGANISM DISCOVERED	NO. OF STUDENTS WITH POSITIVE STOOLS ON DEPARTURE	NO. OF STUDENTS WITH POSITIVE STOOLS ON RETURN	NO. OF STUDENTS WITH NEGATIVE STOOLS ON RETURN
*E. histolytica**	8	6	2
E. coli	17	10	7
G. lamblia	2	0	2
One or more protozoa	50	32	18

*Includes probably positive specimens.

One student in the nonpaired group had *Heterodera marioni* eggs *(Oxyuris incognita)* in his stool on the return trip, and another in the same group had *Trichuris trichiura* eggs. There was no other evidence of the acquisition of helminthic disease, and the students may have had these infections before going to Europe.

On one of the returning vessels approximately 200 students who provided specimens were asked to indicate if they had had diarrhea abroad; 153 responded. Fifty-two per cent of the students in the paired group and 67 per cent in the nonpaired group reported an attack of diarrhea (Table 5).

TABLE 4. *Results of Examinations of Students (Paired Group) with Positive Stools on Return Trip.*

ORGANISM DISCOVERED	NO. OF STUDENTS WITH POSITIVE STOOLS ON RETURN	NO. OF STUDENTS WITH POSITIVE STOOLS ON DEPARTURE	NO. OF STUDENTS WITH NEGATIVE STOOLS ON DEPARTURE
*E. histolytica**	12	6	6
E. coli	22	10	12
G. lamblia	6	0	6
One or more protozoa	61	35	26

*Includes probably positive specimens.

An effort was made to distinguish between students who visited the cooler and presumably better sanitated portions of Europe and those who visited the warmer and supposedly poorer sanitated countries (Table 5). To establish two groups more or less equal in size the replies were divided into the Mediterranean area (students who visited Italy, Spain, Yugoslavia, Israel, Morocco, Portugal, Africa, Greece, Syria, Leba-

non, Egypt, Algeria and Turkey, as well as those who may have visited some non-Mediterranean countries) and the non-Mediterranean area (students who visited France, Germany, England, Switzerland, Holland, Belgium, Austria, Denmark, Sweden, Norway, Scotland, Ireland, Luxembourg and Finland — excluding those who visited countries listed as Mediterranean).

Seventy-one per cent of those in the Mediterranean group had diarrhea whereas 50 per cent of the non-Mediterranean group had diarrhea (Table 5).

The listing of France in the non-Mediterranean group was, of course, arbitrary, but if it had been otherwise listed the groups in Table 6 would not have been approximately equal. An analysis of students who visited France showed the incidence of diarrhea to be halfway between the Mediterranean and non-Mediterranean frequency. If France was shifted to the Mediterranean groups 67 per cent of the Mediterranean group had diarrhea and only 35 per cent of the non-Mediterranean group had diarrhea (Table 5).

TABLE 5. *Prevalence of Diarrhea.**

CLASSIFICATION	MEDITERRANEAN AREA		NON-MEDITERRANEAN AREA	
	STUDENTS WITH DIARRHEA	STUDENTS WITHOUT DIARRHEA	STUDENTS WITH DIARRHEA	STUDENTS WITHOUT DIARRHEA
Paired Group	25	9	4	18
Nonpaired Group	36	16	29	16
Totals	61	25	33	34
Totals†	85	42	9	17

*Based on 153 responses.
†Including France in Mediterranean group.

Table 6 indicates the difference in the acquisition of intestinal parasites between students who visited the Mediterranean countries and those who limited their vacations to the non-Mediterranean countries. If France had been included in the Mediterranean group no significant change in Table 6 would be apparent.

DISCUSSION

The data indicate that there was no major acquisition of intestinal protozoa by students who spent two months traveling in Europe (Table 2). Although the total figures showed a slight increase in the incidence of protozoal infections after the vacation no major public-health threat was suggested.

Nor is it possible to attribute the diarrhea reported by more than half the travelers to protozoal disease. It is noteworthy that whereas the frequency of protozoal infection in students who visited the Mediterranean countries was similar to that in those who visited only the non-Mediterranean countries (Table 6), there was considerable difference in the occurrence of diarrhea (Table 5).

Although no positive statement is justified this evidence suggests that the diarrhea of the continental traveler is not due to fecal contamination of water and food by *E. histolytica* — and by inference not due to salmonella or shigella organisms — but is probably caused by ingestion of foods containing toxins such as those produced by the staphylococcus. The warmer climate and poorer refrigeration of the Mediterranean countries may be major factors in this postulated prevalence of food poisoning. Other possibilities are, of course, not excluded as explanations for the diarrhea of tourists, and the bacterial infections are too important to be eliminated on theoretical grounds alone.

The incidence of parasites in this group of healthy young people from all parts of the country is interesting. If the figures in our tables are used approximately 4 per cent of the students in the United States harbor *E. histolytica* and approximately 25 per cent have one pathogenic or nonpathogenic protozoan parasite in the stool.

Before these figures are accepted it would be well to evaluate the efficiency of a single examination of a casual stool specimen. Most studies have revolved about the efficiency of the diagnosis of *E. histolytica* infections. Wenyon and O'Connor[7] reported that a single stool examination revealed 30 per cent of infections; Dobell[8] thought the proper figure was 40 per cent. Brown[9] considered the initial examination 68 per cent efficient. More recently Sodeman[10] stated that a single examination of a casual stool specimen uncovers only 20 per cent of amebic infections; this view is in harmony with the statistical studies of Sawitz and Faust.[11] It seems reasonable, therefore, to assume that our single examination exposed no more than 50 per cent of the persons who actually harbored protozoal infections.

TABLE 6. *Distribution of Parasites in Returning Students.**

ORGANISM DISCOVERED	STUDENTS IN MEDITERRANEAN GROUP WITH PARASITES†	STUDENTS IN NON-MEDITERRANEAN GROUP WITH PARASITES‡
E. histolytica§	8	8
E. coli	17	16
E. nana	18	18
D. fragilis	4	5
I. butschlii	5	1
G. lamblia	10	2
One parasite	36	32
One or more parasites	49	40

*Excludes students in paired group with positive stools on way over and on return; hence figures do not match those in Table 2.
†Total of 180 students in group as whole.
‡Total of 190 students in group as whole.
§Includes probably positive specimens.

If the conservative statement that repeated examinations under ideal laboratory conditions would double the number of parasites found in a single examination is accepted, 8 per cent of the American students are infected with *E. histolytica*. This figure is in har-

mony with the estimate that 10 per cent of the entire population of the United States is infected with that parasite.[12] It is possible, of course, that the specimens obtained did not represent an adequate sample of the student population, but we believe that the sampling was reasonably scattered and reflected the general prevalence of amebiasis.

Six students (2.7 per cent of 222) were considered to have acquired amebiasis abroad (Table 4). It is likely that the re-examination of 222 students who took their vacations anywhere in the United States would reveal an equally high percentage. Some of these 6 students may have had their infections before reaching Europe since only a single examination was done.

Giardiasis is a relatively common infection on the European continent[13] and is thought by some to be a cause of acute diarrhea. Although 6 students, or 2.7 per cent (Table 4), became infected this fact can hardly explain the enteritis of tourists. It may be of significance that 5 of these 6 students had visited the Mediterranean area.

The importance of *Blastocystis hominis* in the stool is not clear.[14] The late Dr. F. W. O'Connor[15] believed that this fungus was an indication simply of diarrhea, of any cause either current or recent; he did not consider *B. hominis* pathogenic. Since a fourth of the students had *B. hominis* in their stools on both the trip over and the return and since there was no increase on the return trip, although half the students reported episodes of diarrhea, we are inclined to minimize the significance of its presence in stool specimens.

The absence of leukocytes in the stools (Table 2) indicates that the diarrhea that affected many of the travelers did not produce a persistent colitis.

Summary

In an effort to determine how much amebiasis and other protozoan infection is acquired by American tourists in Europe 804 stool specimens from 582 different persons were examined. The stools were obtained from 222 American students who provided "paired" specimens before and after a two months' vacation in Europe during the summer of 1953 — and also from 360 other students, 180 of whom cooperated en route to Europe and 180 others who supplied "nonpaired" specimens during the return voyage.

No major increase of *Endamoeba histolytica* and other intestinal protozoa occurred, and no evidence was obtained that travelers to Europe acquire sufficient protozoan disease to present a public-health hazard on their return.

Over half the tourists had diarrhea during their two months' stay in Europe. The frequency of diarrhea was considerably higher in those who visited the Mediterranean countries than in those who visited only non-Mediterranean countries. There was, however, no significant difference in the occurrence of protozoal infection in these two groups of travelers.

It is suggested that the diarrhea of the continental traveler is not due to the fecal contamination of food and water but is more probably caused by the ingestion of toxins such as those produced by staphylococci.

No evidence for the acquisition of helminthic infections was obtained.

The frequency of *E. histolytica* infection of healthy American students on a single stool examination was 4 per cent, and the total prevalence of protozoan infection was 25 per cent.

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MEDICAL PROGRESS

PHYSIOLOGIC PSYCHOLOGY OF NEUROSIS*

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This *Section* is attended with much more Difficulty as to its Explanation, than any of the former; because the *Propositions* herein contained are not demonstrable in the same Manner as those which relate only to the Agency of physical Causes. For as it was before taken Notice of, the Operations of the Mind upon the Body, and *è contra*, do not come under a mechanical Way of reasoning; it being impossible to decypher and trace out the several Steps and Ways of Procedure of those Agents, which can by no means be brought under the Cognizance of our Senses. In Enquiries therefore of this kind, there must be allowed some farther *Data* than need be in such as are merely physical. . . . (Sanctorius: *De Statica Medicina*, 1614).

NEUROPHYSIOLOGY OF ANXIETY

MUCH of what is currently believed about the feeling of anxiety in man is based on introspective analysis of the feeling by psychologists and psychiatrists. However, certain interesting data on the somatic aspects (not effects) of anxiety have come to light during the past decade.

It is well known that severe anxiety occurs in association with some epileptic seizures that originate in temporal-lobe foci[1,2]; the fact that persistent or recurrent anxiety develops after trauma to this area has also been emphasized.[3] These suggestive findings become more significant in the light of recent observations by Penfield and his associates.[4] These workers have found that stimulation of the lower temporal lobe in man may produce anxiety and also certain vague epigastric and precordial symptoms that resemble those associated with spontaneous anxiety.

Experiments made in animals by several authors a few years ago suggested that the functioning of the autonomic nervous system was an important factor in the establishment and maintenance of conditioned reflexes that involve fear. Solomon and Wynne[5] observed abnormally rapid extinction of such reflexes in a few dogs that had been subjected to sympathectomy; however, the experiments were too few in number to yield satisfactory data. Auld,[6] in a study of rats given tetraethylammonium salts, observed reduced responses in a learned behavior pattern motivated by fear. However, Brady[7] and Davitz[8] could not confirm these findings; they ascribed any behavioral changes that occurred to the general depressing action of the drug. Sympathectomy, chemical or surgical, does not affect behavior motivated by fear; thus it is evident that the integrity of the sympathetic nervous system is not a general determinant of such behavior. However, the action of sympathetic nerves in stimulating the release of epinephrine constitutes an important mechanism in the causation of anxiety; this is discussed below.

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PHARMACOLOGY OF ANXIETY

The development of anxiety in subjects given epinephrine by injection is a well known phenomenon.[9] It is particularly interesting because many of the somatic changes that occur in association with spontaneous anxiety closely resemble various clinical and physiologic effects of the hormone.[10] Several concepts have been advanced to explain this relation, but there is no information that conclusively defines it. Allegations, such as those of Ax,[11] that epinephrine alone is released during fear and that both epinephrine and norepinephrine are released during anger, are not supported by substantial data. Injections of epinephrine that cause anxiety do not change cerebral blood flow or oxygen consumption.[9] Injection of an adrenolytic substance that acts only on peripheral blood vessels does not prevent the anxiety produced by endogenous epinephrine called forth by hypoglycemia[12]; however, administration of hexamethonium, which prevents the reflex liberation of epinephrine, does prevent anxiety caused by hypoglycemia.[13] This effect is observed even in patients with anxiety neurosis. The anxiety associated with pulmonary embolism also is allayed by blocking agents of this general type,[14] but this phenomenon may have a variety of explanations. However, the excellent studies of Laurence and Stacey[13] establish the fact that inhibition of the action of the sympathetic nervous system on the adrenal medulla prevents anxiety in some circumstances.

The anxiety-producing action of epinephrine is not directly related to its hypertensive effect. This is shown by the fact that anxiety develops during hypoglycemia even when the action of epinephrine on blood vessels is suppressed.[12] In addition, ephedrine may cause anxiety when taken by mouth in doses not large enough to raise the arterial pressure. Moreover, another sympathomimetic amine, methoxyphenamine, produces anxiety but lowers arterial pressure somewhat. Mono- or dimethoxy (or ethoxy) phenylethylamines also cause outward manifestations of marked fear when injected in animals.[15] These effects may prove highly significant, since these compounds resemble degradation products of epinephrine.

The degradation of epinephrine is not completely understood.[16-18] Little, if any, of a dose of injected

epinephrine is excreted in the urine unchanged or in a conjugated form. The fate of the remaining quantity is not known. Although the amine oxidase system has been shown to destroy epinephrine in vitro, the significance of this reaction in man is not established. Excellent experiments by Schayer[19,20] show that during the ultimate disposal of epinephrine in the rat and the rabbit about half the injected dose (or of its degradation products) is broken down by amine oxidase. However, these facts about ultimate disposal four to sixteen hours after injection throw no light on the mechanism of initial inactivation. Indeed, epinephrine, in contrast to some other sympathomimetic amines, is a poor substrate for amine oxidase.[18,21]

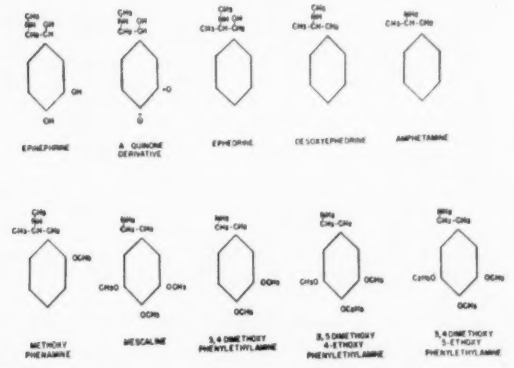

FIGURE 1. *Epinephrine and Some Chemically Related Compounds That Are of Psychiatric Interest.*

Moreover, Schayer's observations in rats and rabbits may not be entirely applicable to man or to dogs, the metabolism of sympathomimetic amines being different in these species from that in rodents. Another enzyme, catechol oxidase, is believed to transform epinephrine into an orthoquinone (Fig. 1) and ultimately into other compounds.[16,18] The possibility that this orthoquinone is further transformed into methoxy- or ethoxyphenylethyl amines in the body must be borne in mind. An additional point for speculation is whether such compounds might be produced in excess during oversecretion of epinephrine, or as a consequence of some disturbance in the mechanism for inactivating that hormone. At any rate, if these methoxy (or ethoxy) phenylethylamines accumulated abnormally, anxiety would probably occur, with or without coincident rises in arterial pressure.

The mechanism whereby sympathomimetic amines or the related methoxy (or ethoxy) phenylethylamines cause anxiety is not known. However, at least some compounds of this type are known to act centrally; their chief effect is the inhibition of transmission.[22] Clinical examples of the central effects of these compounds are afforded by the mental changes caused by 3, 4, 5, trimethoxy-phenylethylamine (mescaline), amphetamine and desoxyephedrine. An interesting hypothesis can be created to the effect that although prolonged excessive production of epinephrine might result in tolerance to its somatic effects, it might under some conditions cause the accumulation of toxic substituted quinones or related substances that cause psychosis by adversely affecting cerebral function.

Available evidence suggests that epinephrine, or some derivative of it, causes feelings of anxiety through a central action that is independent of pressor effects. There is nothing to indicate that this is the only mechanism for the production of these feelings; it is quite probable that anxiety also arises through direct neurogenic stimulation of the area localized by Penfield's group.[4]

EFFECTS OF ANXIETY ON CONDITIONED REFLEXES AND LEARNING

Discussion of psychologic mechanisms in anxiety is beyond the purpose of this review; clearly presented summaries of available information have been written by Hanfmann[23] and by Lazarus et al.[24]

Studies on subjects who either were experiencing anxiety or had been diagnosed as neurotic or unstable revealed that the establishment of conditioned reflexes is usually accelerated in such persons.[25-37] Delayed extinction alone was noted by some workers[38] or was found in association with increased ease of conditioning.[26,28,36] Discrimination was uniformly found to be decreased in these subjects[26,34,38-40]; conditioned responses occurred in them when they were given stimuli that were too different from the conditioning stimulus to cause such responses in normal subjects. The conditioned-reflex reactions in anxious subjects are even stronger on retesting after longer, rather than shorter, periods of rest[41,42]—that is, reactions associated with anxiety may incubate.

Some general aspects of conditioning should be kept in mind. Voluntary and conscious mental attitudes do not significantly affect the phenomenon.[43] The intensity of the *conscious* reaction to the stimulus is very poorly correlated with the intensity of the *conditioned* reaction[29]; indeed, conditioning can occur even when the subject shows no grossly visible sign of responding to a stimulus.[44] Merely thinking about the stimulus may evoke the conditioned-reflex response.[45] In general, autonomic responses may follow stimuli that have been presented too quickly to be consciously recognized[46]; in particular, conditioned reflexes have been observed after presentation of stimuli that are not consciously perceived.[47-49]

The fact that sensory stimuli that are above the absolute threshold can cause autonomic reactions without the subject's consciously recognizing or even being aware of the stimuli is pertinent to the problem of "perceptual defense." This concept has been used in experimental psychology to explain the finding of elevated visual and auditory *recognition* thresholds for unpleasantly toned stimulus words. However, some clinicians had previously introduced a similar but

broader concept to explain patients' unawareness of a variety of environmental stimuli. Both concepts—the narrow psychologic concept of "perceptual defense" and the broader related clinical concept—imply that one segment of the mind acts as an executive organism that willfully regulates recognition and decides what other segments of the mind shall know. Discussion of any such philosophic problem is beyond the purpose of this review. It is sufficient to point out here that even the limited experimental psychologic concept of "perceptual defense" is controversial and is not supported by the bulk of available evidence.[50]

The problem of whether stimuli below the absolute sensory threshold can act as conditioning stimuli or can cause a conditioned response after establishment of the reflex has important clinical implications. There is good evidence that visceral changes may be evoked by sensory stimuli below the absolute threshold.[51] However, earlier work[52,53] that apparently showed that such stimuli might cause conditioning of the pupillary reflex has not been corroborated.[54,55] In agreement with this fact, experiments with several other types of reaction[55-57] have demonstrated that subthreshold intensities of stimulation do not cause responses when conditioning to suprathreshold stimuli has been established.

The complexity of the general problem of conditioning is increased by the fact that a phenomenon called "sensory preconditioning" may occur.[58-61] An example is as follows:

> Two stimuli, a tone and a light, are repeatedly paired in the first stages of training, and in the second stage one of these stimuli, say the light, is paired with shock to the forelimb until it comes to elicit a flexion response. Finally the tone is presented alone and the flexion response appears despite the fact that tone and flexion have never before occurred in temporal contiguity.[58]

This reaction, first described in the rat, has also been shown to occur in man.[59,60]

Learning of voluntary verbal and motor responses may be related, in respect to mechanism, to the conditioned reflex. Studies in rats uniformly show that fear accelerates the learning of reactions that help to reduce fear—that is, fear acts as a drive in certain types of learning.[62-66] However, other previously learned responses are inhibited by fear in these animals, and the general pattern of behavior may become disorganized.[67-69] The applicability of these animal experiments to human learning and habit formation has not been established. Observations in man show that learning in anxious persons is accelerated with respect to simple tasks with high associative content[70] or at times when stress can be avoided by learning[71]; however, it is retarded in all other circumstances studied.[35,71-78] The manifestation or the development of perseveration and rigidity in thinking and problem solving during stress is an interesting finding.[79-83] The comment of Tolman and Postman[84] is worthy of note:

> We feel that the effects of failure, stress, and related conditions on learning and retention can for the present be adequately and parsimoniously handled by the more mundane concepts of current learning theories. The invocation of ego defense or repression seems to put too heavy a conceptual burden on rather slender empirical facts.

The importance of knowing as much as possible about conditioned reflexes and learning processes in emotional disorders requires no emphasis; no hypothesis that attempts to explain how emotional disturbance leads to the development of persistent abnormal patterns of behavior or of reflex visceral function can be valid unless it includes consideration of such phenomena. Acquisition of clinical data of this type is extremely difficult; however, one cannot solve the problem by ignoring it. Skinner's[85] comments summarize one of the difficulties:

> In the field of behaviour a science must contend with an extraordinary richness of experimental material. The number of stimuli to which it may come to respond . . . is indefinitely large, and to each of them it may be made to respond in many ways. It follows that the number of possible reflexes* is for all practical purposes infinite and that what one might call the botanizing of reflexes will be a thankless task. Nevertheless, there is no way of reaching the goal . . . except to botanize . . . .
>
> We have no reason to expect, either from theoretical considerations or from a survey of what has already been done experimentally, that any wholesale prediction of response or identification of stimulus will become possible through the discovery of principles that circumvent the routine of listing reflexes.*

Studies of the clinical significance of conditioned reflexes and related reactions in neurosis would necessitate a great collection of standard stimuli—sights, sounds, smells and so forth—that could be presented under carefully controlled conditions to patients in whom vasomotor, cardiomotor, sudomotor, respiratory and gastrointestinal functions, singly or together, were under objective study at the time. The cost in time and money of such a project would be high, but these expenditures would be no greater, and might be more fruitful, than current expenditures for merely listening to patients.

One group of studies, in animals, has provided interesting data on the effects of electroshock therapy on instinctive behavior[86,87]; disorganization of an instinctive behavior pattern occurred. Other animal experiments have shown weakening or loss of conditioned responses after convulsions induced electrically or otherwise[88-94]; the loss lasts about a month. (This period approximates the interval that passes before relapse occurs in some patients given this form of therapy.) However, induction of more seizures over a longer period may prolong the effect of electroshock on conditioned reflexes in rats.[95]

Emotion in Etiology of Certain Somatic Diseases

The history of medicine from its earliest days to the present reveals that diseases of unknown etiology have often been ascribed to emotion. Clinical obser-

*Skinner uses the word "reflexes" here to indicate any stimulus-response relation.

vation of an apparent relation between emotional upset and *exacerbation* of hypertension, arthritis, bronchial asthma, peptic ulcer, thyrotoxicosis, ulcerative colitis and some cutaneous disorders has led some psychiatrists to conclude that emotional upset is the *cause* of these diseases.

Various concepts have been suggested to explain how emotion may have this effect. Symbolic explanations belong in the realm of analogic magic and need not be discussed here. Many publications that describe the cause of one or another of these diseases as some specific personality conflict have no substantial validity. Weiss et al.[96] recently concluded that hypertension was not caused by such personality patterns or conflicts, thus confirming Hamilton's[97] earlier statistical study, which has largely been ignored. Papers that attempt to relate personality to various types of autonomic function still appear[99]; most are characterized by limited data and comprehensive conclusions. A recent paper[100] differs from most of the others in that the author concludes conservatively that his data reveal no relation between personality and autonomic reactivity.

Another explanation, much favored by some psychosomaticists, involves concepts advanced by Selye in his theory of the "general adaptation syndrome"; this is that emotion "derails" normal pituitary-adrenocortical function and thereby leads to the development of arthritis and vascular disease. At a symposium on this matter held last year[98] Selye defended his thesis but offered no data. Ingle and Baker[98] and Clark and Bauer[98] reviewed pertinent physiologic data and concluded that serious doubt of the role of the "general adaptation syndrome" in these diseases was justified; these conclusions support the skepticism that some internists have felt for some time.

I do not mean to deny that altered adrenocortical and medullary function may exacerbate the diseases mentioned above and also some others; data bearing on this matter have been reviewed elsewhere.[10] The fact that recent work by Thorn et al.[101] demonstrated no adrenocortical hyperactivity during emotional stress does not invalidate this concept, since these authors used a mild and short-lived stress in their experiments. Similarly, the finding in man that epinephrine does not activate the adrenal cortex[101-104] does not negate the importance of the adrenal cortex in emotion.

Another explanation of some psychosomatic relations is based on the belief that there are individual patterns of autonomic response to emotion that are inborn or are acquired as conditioned reflexes. An excellent study made by Brunswick[105] some years ago showed that gastrointestinal motor patterns varied with emotion but were constant in individual subjects studied. More recent work by Lacey[106-109] and by Terry[100] showed that a few other emotional autonomic responses evoked by several simple stresses showed persistent patterns in various persons. These observations support clinical impressions but do not explain the origin of these patterns. A recent study in infants[110] provides data that support the idea of inherited patterns; the authors of a study on rats[111] reached similar conclusions. These deductions do not rule out the possibility that there are also patterns of reaction that are acquired early in life.

The somatic changes associated with mental effort and even with concentrated attention are identical with those caused by emotion; the reported somatic effects of thoughts, feelings and emotions are all the same. Perhaps the chief cause of the somatic reactions associated with these phenomena is mental activity alone (not necessarily *conscious* mental activity), and perhaps emotion is the most important category of such activity only because it apparently occurs more frequently and is usually more intense than the others. This concept raises the possibility that present-day psychiatric preoccupation with the specific emotional coloring, rather than the nonspecific intensity, of mental phenomena is somewhat misguided.

The problem of the relation of emotion to the exacerbation of a variety of somatic diseases is complex and difficult; it will ultimately be solved through conclusions based on accumulated data.

Many studies of physiologic changes related to emotion have been published since the last review[10] was written. Cardiovascular phenomena have engaged the attention of many observers. The tachycardia of emotion has been investigated further.[112] More cases of arrhythmias precipated by emotion have been reported.[113-116] Further studies on the rise of arterial pressure during emotion have been made.[116,117] The idea that despair lowers arterial pressure[117] has been criticized elsewhere.[10*] Vasoconstriction and small localized increases in venous pressure occur with emotion[121]; however, venous pressure as a whole does not change in normal subjects during emotion but does rise in patients with cardiac decompensation.[122] A thorough study by Lenègre et al.[123] shows that pulmonary capillary and arterial pressure do not change during anxiety in normal subjects, whereas patients with pulmonary edema show increases in both in association with anxiety; their cardiac outputs rise only slightly, in contrast to those of normal subjects, which rise greatly.

The pattern of acral cutaneous vasoconstriction with vasodilatation over the head and upper trunk has been discussed elsewhere.[10] Recent work has provided further data on the action of epinephrine in diminishing blood flow in the hand[124]; this vasoconstriction is followed after a time by reflex vasodilatation. The importance of the common but inconstant occurrence of dilatation of blood vessels in the muscles of the arm and leg has not been emphasized suffi-

*The belief that specific emotions have specific effects on the circulation dates back to ancient times and is still generally accepted in parts of the world where Galen is the ultimate authority. Work done in this country half a century ago showed that the circulatory changes of emotion were independent of the quality of the emotions.[118-120] The physiologic effects of unpleasant emotion apparently last a little longer than those of pleasant emotions.

ciently. Three excellent papers by Wilkins and Eichna[125-127] describe this phenomenon. An immediate neurogenic dilatation occurs in response to emotion, and is followed by a slower epinephrine-induced vasodilatation.[125,128] This phenomenon is apparently different from the dilatation of the blood vessels of the arm that occurs during hyperventilation.[129]

Cutaneous blood flow over the arm may also increase during emotional stress. This phenomenon, which Graham and Wolf[130] earlier correlated with a tendency to urticaria, was recently linked by these authors to the occurrence of eczema.[131] Their specific symbolic interpretation of the vasodilatation was not the same for both syndromes.*

Studies of changes in rate and depth of respiration in neurosis show that both are likely to increase with various emotions.[132] In addition to the papers mentioned in connection with conditioned reflexes, other publications on the psychogalvanic response (which measures sweat-gland activity) have appeared. The test has apparently been standardized.[133] A good review of the application of the procedure recently appeared,[134] and additional observations on the changes observed during psychologic stress have also been published.[135] A curious bioelectric phenomenon that varied with emotion in man and with phases of the moon in man and in elm, oak and maple trees in New Haven has been described.[136] Observations on the apocrine sweat glands revealed that their activity increased in frightened or excited patients[137]; epinephrine had a similar effect, but an increase in temperature did not. Recent experiments by Robin and Kepecs[138] on secretion of sebum confirmed earlier work on the role of emotion. These authors correlated the changes with symbolic factors that differed from those described by previous workers. The mechanism of the change in secretion of sebum is not clear, since the sebaceous glands—in man, at least—are believed to have no innervation.[139] Perhaps the facial vasodilatation induced by motion is the responsible factor.

The effects of emotion on gastrointestinal function have been studied by several groups. The symbolic explanation that peptic ulcer is due to a hunger for affection is not borne out by the studies of Bachrach et al., [140] who found no relation between the occurrence of pain and the development of hunger contraction in patients with duodenal ulcers (the motor pattern induced by hunger was usually normal). Thorough studies by Little[141] lent scant support to the idea of Eppinger and Hess[142] that peptic ulcer was due to a generalized state of autonomic imbalance. The authors of a recent study[143] concluded that anxiety caused gastric hyperacidity. They studied the gastric juice every hour for thirteen hours on two consecutive days in 10 subjects and concluded that higher values occurred on the second day. However, statistical analysis of their data on gastric free acid secretion showed that many of the changes were insignificant:

Comparison of the Two Days as a Whole in Each Patient

P value	0.01 in 5 patients
P value	0.05 in 1 patient
P value	>0.05 in 4 patients

Comparison of the Two Days Hour by Hour in All Patients

P value	0.01 in 1 hourly period
P value	0.05 in 6 hourly periods
P value	>0.05 in 6 hourly periods

The changes were not constant enough to be regarded as a demonstration of the action of any simple factor. Moreover, no evidence was presented to prove that these questionable changes were due to anxiety rather than to anger, resentment and so forth. Furthermore, recent work[144] minimizes the importance of gastric hyperacidity as the cause of peptic ulcer.

The motor pattern of nausea and vomiting was described by Abbott et al.[145]; this pattern was not found in patients with neurotic vomiting. Observations by Jackson[146] on an isolated loop of jejunum showed no changes in motility or color during emotion. Studies made with balloons by Roth et al.[147] on the effects of emotion demonstrated motor changes in the small intestine in about 20 per cent of the experiments; no correlation with type of emotion or even with the occurrence of pain was found.

Studies of pelvic blood flow, made with a poor method, were said to show increases during anxiety or resentment.[148]

Changes in neuromuscular function in relation to emotion have been observed in several clinics. Increased electromyographic activity has again been shown to be caused by emotion[149,150]; the relation of these changes to muscle aches and some types of headache seems clear. Unconscious emotional reactions may reveal themselves by changes in the electromyogram.[150] A study of the blink rate suggests that anxiety (as evaluated by a score in a test) has no effect whereas maladjustment increases it[151]; perhaps these scoring methods should be reassessed. The effect of epinephrine in increasing tremor in Parkinson's disease[152] apparently explains the heightened tremor caused by emotion; epinephrine is known to have central actions.[22] Reaction time is slowed by anticipation of pain[153]; this phenomenon is reversed by morphine. Anxiety inhibits muscular aftercontraction.[154] Interesting studies on the effect of hyperventilation in making painless cutaneous lesions painful[155] may have great clinical importance.

Callaway and Thompson[99] showed that activating the sympathetic nervous system by suddenly chilling a limb caused subjects to describe distant objects as closer than they were; earlier work by Hastings[156] had shown that insecure persons also described objects as closer. Such studies involve judgment and not per-

*This clash of symbols is one example of the discords frequently encountered in the psychosomatic literature.

ception. Effects of anxiety on sensory perception were discussed in an earlier work.[10]

Two excellent works that recently appeared should be read by all who wish to understand the central neurophysiologic background of emotion; these are the publications of Yakovlev[157] and Cobb.[158] A series of five papers on the neurophysiology of consciousness[159-163] will prove highly informative as well as interesting to the general medical reader.

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MEDICAL INTELLIGENCE

TUBERCLE BACILLI IN LUNGS RESECTED FROM TUBERCULOSIS PATIENTS*

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THIS report on the tubercle bacilli recovered from the resected lungs of patients with proved tuberculosis consists of an analysis of 100 consecutive surgical specimens removed by surgical excision of residual pulmonary tuberculosis in 100 patients.

Eighty-seven patients had received two drugs (dihydrostreptomycin, 1 gm. intramuscularly twice each week, and para-amino-salicylic acid, 12 gm. daily in three divided doses) for six months or longer before operation. Most of these patients also had received iso-nicotinic-acid hydrazide, 100 mg. three times daily, before operation. Fifty-four (62 per cent) of these specimens were negative on slide, culture and guinea-pig examination for tubercle bacilli; 38 per cent were positive for tubercle bacilli (Table 1).

Thirteen patients had not received the specific antituberculosis drugs before resection. Eight (61.5 per cent) of these were negative on slide, culture and guinea-pig examination: 5 (38.5 per cent) were positive (Table 2). The number of these patients may be insufficient for statistical purposes. Also, most of the lesions in this group consisted of tuberculomas and were clinically indistinguishable from tumor. However, it is interesting that approximately the same percentage of lung specimens in the latter group of patients was negative for tubercle bacilli as in those who had received adequate specific therapy preoperatively.

TABLE 1. *Results of Study in Patients Who Had Received Specific Drugs for Six Months or Longer.*

EXAMINATION OF RESECTED LUNG FOR TUBERCLE BACILLI	NO. OF PATIENTS	
Negative on slide, culture & guinea-pig inoculation	54	(62.1%)
Positive on slide only	15	(17.2%)
Positive on slide, culture & guinea-pig inoculation	9	(20.7%)
Positive on culture & guinea-pig inoculation only	7	
Positive on culture only	2	
Total	87	

TABLE 2. *Results in Patients Who Had Received No Specific Antituberculosis Drugs.*

EXAMINATION OF RESECTED LUNG FOR TUBERCLE BACILLI	NO. OF PATIENTS
Negative on slide, culture & guinea-pig inoculation	8(61.5%)
Positive on culture & guinea-pig inoculation	3
Positive on slide only	1
Positive on guinea-pig inoculation only	1
Total	13

The laboratory work was carried out by the State Health Department, Lansing, Michigan.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 40371

PRESENTATION OF CASE

First admission. A seventy-six-year-old widow was referred to the hospital for consideration of gastric operation.

The patient had been well until recently when she noticed an aching sensation in the back brought on by walking or sitting for long periods. She visited her physician, who found a stool to be guaiac positive. A subsequent gastrointestinal series revealed a polypoid growth on the greater curvature of the stomach.

Physical examination, which showed a very well preserved woman, was negative.

The temperature, pulse and respirations were normal. The blood pressure was 180 systolic, 90 diastolic.

Routine laboratory studies were normal; the blood hemoglobin was 12.6 gm. per 100 cc., and the prothrombin time 16 seconds (normal, 14 seconds). An electrocardiogram was normal.

On the second hospital day a subtotal gastrectomy was performed. Because of the mild anemia she was given 1 transfusion during the operation. The pathological report on the surgical specimen was polypoid adenocarcinoma, Grade 2; the regional lymph nodes were negative for tumor. The postoperative course was uneventful; she was discharged on the fourteenth day.

Second admission (six months later). She stated that she had felt very well until six weeks before admission, when she experienced paresthesia in the left hand. Since then she had noted intermittent pains in both arms that were relieved by heat and aspirin. One week before entry she began to feel nauseated and lost her appetite. At that time she was observed to be jaundiced. Two days before admission the nausea became nearly constant. The urine had been dark for about a week. No change in stools was noted, there was no vomiting, melena, chills or fever. There was no pain or itching.

Eight years before admission she had had an attack of "acute cholecystitis," and three years later she had a second attack, with severe right-upper-quadrant pain, fever and jaundice. She had been hospitalized and a cholecystotomy performed, with removal of stones. Postoperative x-ray films were said to have shown that "the duct was clear." There had been no recurrence of symptoms since the operation.

Physical examination revealed a mildly icteric woman who was in no distress except for moderate nausea. The chest was clear; the heart was normal. In the abdomen there were well healed right-upper-quadrant and midline scars. The liver was palpable 4 cm. below the right costal margin and had a round, firm edge but apparently was not tender. The spleen was not palpable.

The temperature, pulse and respirations were normal. The blood pressure was 165 systolic, 90 diastolic.

The urine was cloudy amber, had a specific gravity of 1.027 and gave a + test for albumin and a negative test for bile; the sediment contained 10 white cells per high-power field. The urinary urobilinogen was 1.9 Ehrlich units. Examination of the blood revealed a white-cell count of 8500, with 63 per cent neutrophils. The alkaline phosphatase was 8.4 units, the thymol turbidity 3.5 units, and the total serum bilirubin 6.6 mg. per 100 cc. The prothrombin time was 14 seconds (normal, 13 seconds); the thymol flocculation was negative, and the cephalin flocculation was ++ in twenty-four and +++ in forty-eight hours. A stool specimen was light brown and guaiac negative. A plain film of the abdomen and a spot film of the gallbladder region failed to show opaque stones either in the gall bladder or along the urinary passages. In addition, no abnormal masses or enlarged viscera were noted. A gastrointestinal series disclosed that a proximal subtotal gastrectomy had been done, with removal of about half the stomach. There was no delay in the entrance of barium into the stomach or in gastric emptying. No definite local neoplastic recurrence was seen.

In the hospital there was little change clinically although nausea diminished after about a week. No new symptoms developed. The temperature continued to be normal; the liver size was unchanged, and the jaundice persisted. On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES H. DU TOIT*: This is a problem of diagnosis in an elderly woman who was admitted to the hospital with jaundice six months after the apparently successful resection of a carcinoma of the stomach. The symptom of pain in the back, the only unusual feature noted on the first admission, does not seem obviously related to the gastric cancer unless the lesion had already spread at that time. This symptom, however, seems to have disappeared in the interim. Therefore, I will not give it any further consideration.

Three things in the past history could have had a

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bearing on the present illness. The first is the transfusion. I assume that about a hundred and seventy days elapsed between the transfusion and the appearance of the jaundice. If we take into account the vague symptoms six weeks before admission, we might conceivably shorten the latent period to a hundred and thirty days. Even that interval was a little longer than the usual latent period of serum hepatitis. One wonders if the patient, at a more recent date, had had any venipunctures or parenteral injections. The second feature of the past history is the removal of gallstones without removal of the gall bladder. The third part to consider as a possible factor in the jaundice is the cancer of the stomach.

Searching the history of the present illness for possible clues, I was struck immediately by the loss of appetite and the nausea, which coincided with the observation of jaundice by the patient. Since she dated the onset of that symptom, I can assume that it was fairly acute. This history strongly favors viral hepatitis over any other diagnosis. Of course this was an elderly person, and diseases in the elderly often fail to follow the textbook description.

This history is conceivably compatible with rapid spread of cancer, either primary or secondary, throughout the liver. In extrahepatic obstruction of the biliary tree by stone or tumor, symptoms of this kind are generally due to an ascending cholangitis associated with fever and a high white-cell count. Carcinoma of the pancreas is usually characterized by a more insidious history. I am at a loss to explain the paresthesia of the left hand and aching in the arms that occurred about five weeks before the jaundice. These might be clues to a more generalized process such as widespread metastatic cancer, but no physical findings or x-ray changes to clarify these symptoms were mentioned. The lack of itching, with the marked icterus, is somewhat in favor of intrahepatic disease. Itching is attributed by some to retention of bile acids, which is less prominent in intrahepatic disease than in obstructive jaundice.

The physical findings also favor viral hepatitis in that the liver was moderately enlarged, which it should not be in obstructive jaundice. It was not massively enlarged or irregular as one might expect with advanced neoplastic involvement.

The laboratory work lets me down. Unfortunately, the complete roster of liver-function tests was not recorded—particularly albumin-globulin determinations and the cholesterol and cholesterol-ester values. Moreover, one would like to have had some of the liver function tests repeated since there may be certain changes in the liver-function tests as time goes on, particularly in viral hepatitis.

The absence of bile in the urine, compared to a serum bilirubin of 6.6 mg. per 100 cc., is most unusual. This finding immediately brings the question of hemolytic jaundice into the picture. The hemoglobin value was not recorded in the protocol, so I assume that it was normal. Since the urinary urobilinogen was not greatly elevated, it seems unnecessary to consider hemolysis further.

The stools were light but not clay colored, and since urobilinogen was being formed, obstruction must have been incomplete. The cephalin flocculation was slightly in favor of liver-cell damage, although this kind of borderline test may occasionally appear with many diseases. The alkaline phosphatase was moderately elevated. In extrahepatic obstruction it is usually higher, but there are frequent exceptions. On the other hand the normal thymol studies could be taken as evidence of pure obstruction. However, in about 20 per cent of cases of viral hepatitis, all the flocculation tests may be within the normal range.

I believe this is one of the cases in which the liver-function tests do not carry as much weight as the history and physical findings so that as my first choice I shall pick intrahepatic rather than extrahepatic bile-duct obstruction. It is quite possible that a diffuse spread of carcinoma through the liver could produce a clinical picture such as this, but such occurrences are exceptional. Therefore, I put that diagnosis second to viral hepatitis. In this case there is no reason to suspect chronic liver disease, such as Laënnec's cirrhosis or other infections of the liver.

Among the causes of extrahepatic obstruction of the bile duct is a common-duct stone. The acuteness of the history, the past history of stones and the incompleteness of the obstruction are in favor of this diagnosis. Rarely, metastatic disease may obstruct the common duct. There is a recent report* of a case of this type; however, the author was able to find only 5 similar cases in the literature. Therefore, we have to consider this a very remote possibility.

In conclusion I believe that the clinical features—the nausea, anorexia, jaundice, slight general enlargement of the liver, normal temperature and normal white-cell count—are more in keeping with one of the viral hepatitides than with any other diagnosis.

A PHYSICIAN: What was the operation?

DR. DU TOIT: I imagine that it was a liver biopsy.

CLINICAL DIAGNOSIS

?Carcinoma of stomach, recurrent, with obstructive jaundice.

?Common-duct stone.

?Viral hepatitis.

DR. CHARLES H. DU TOIT'S DIAGNOSIS

Viral hepatitis.

ANATOMICAL DIAGNOSIS

Viral hepatitis.

PATHOLOGICAL DISCUSSION

DR. EDGAR B. TAFT: This patient did have a liver biopsy. We received a very generous portion of tissue, in contrast to what the pathologist is sometimes given,

*Cernock, W. F. Jaundice due to metastatic obstructive lesions. *Ann. Int. Med.* 39:369-371, 1953.

which showed the characteristic features of viral hepatitis. In the portal areas one could see an infiltration of moderate numbers of mononuclear cells, and there was quite a bit of infiltration of the lobules by similar cells, with moderate disruption of lobular architecture. There were occasional necrotic liver cells. Bile stasis was not particularly prominent.

I am sure someone will want to know whether this was infectious hepatitis or homologous serum hepatitis; I must say that we cannot tell the difference. The length of the history in this case suggests that this was not homologous serum jaundice, because an incubation period of six months would be extraordinarily long for that condition. The clinical course would suit either disease.

The patient began to improve very rapidly about ten days after the biopsy. When she was discharged twenty-five days after biopsy, she was no longer jaundiced and felt much better. The lack of bile in the urine was commented on by the clinicians treating this patient. They finally decided that it had been missed in the laboratory examination of the preoperative specimen, because subsequent urine examinations showed large amounts of bile.

DR. DU TOIT: The urine was described as amber.

DR. TAFT: Both the patient and the clinicians noted that it was quite dark.

CASE 40372

PRESENTATION OF CASE

A sixty-six-year-old man was transferred to this hospital because of abdominal pain.

About three weeks previously the patient noticed the onset of substernal pain that seemed to radiate up between the shoulder blades and down each arm to the elbows and was more severe in the left arm. Associated with this was a dull, aching, noncrampy periumbilical pain that occurred daily, lasted several hours and was not related to activity, meals or position. Nausea and vomiting of small to large amounts of bile-stained fluid were associated with the abdominal pain every other day or so. The stools had become loose but were not more frequent than previously. They were frothy, foul and light in color; he had noted flecks of blood on the toilet paper. He had taken aspirin for the pain but had never required stronger medication. His appetite had continued to be good, but he believed he might have lost 5 to 10 pounds in weight. Three days before admission the chest pain had become very severe, and he was admitted to another hospital, where "injections" were required to relieve the pain; pain was not relieved much, if any, by nitroglycerin. During the past several days the abdominal pain had continued unabated although the chest pain had been relieved.

Eleven years before admission he had had "phlebitis" of the right leg that subsided after three days. Three years later bilateral high saphenous-vein ligations and stripping for varicose veins were done. During this admission the blood hemoglobin was 16.0 gm. per 100 cc. He had never had any abdominal operations.

Physical examination showed a well developed and well nourished man with a generalized dusky hue. The veins over the upper trunk were prominent. The lungs were clear. The heart sounds were poor, and there was a loud apical protodiastolic gallop. The abdomen was not tender, and there were no masses or enlarged organs. Peristalsis was hyperactive, with gurgling and some high-pitched sounds. There was ++ edema of the legs.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 80 diastolic.

The urine had a specific gravity of 1.019 and gave a ++ test for albumin; the sediment contained occasional granular and hyaline casts. Examination of the blood revealed a hemoglobin of 21.0 gm. per 100 cc., a red-cell count of 7,280,000 and a white-cell count of 13,600, with 90 per cent neutrophils. The hematocrit was 59 per cent. The blood sugar was 107 mg., the nonprotein nitrogen 28 mg., the total protein 5.1 gm., the albumin 3.2 gm., and the globulin 1.9 gm. per 100 cc. The prothrombin time was 16 seconds (normal, 13 seconds). A stool specimen was guaiac negative. In a roentgenogram of the chest the lungs were clear. The heart was within normal limits in a posteroanterior projection, but fluoroscopically the left ventricle was noted to be slightly enlarged in its outflow-tract portion. A Graham test showed an incompletely filled gall bladder with a suggestive density below the eleventh rib that could have been a gallstone. In a gastrointestinal series the esophagus was normal, but there was a small hiatus hernia that was reduced in the erect position. The stomach contained no secretion, but hyperperistalsis was noted. The duodenum was compressed extrinsically in its first portion. The duodenal loop and upper jejunum were not remarkable except that the jejunum was to the right of the midline, suggesting the possibility of malrotation. Films of a barium-enema study done in the other hospital were interpreted here as normal. An electrocardiogram disclosed a classic pattern of acute anterior myocardial infarction.

During the first two days in the hospital the patient showed little change clinically. He no longer complained of chest pain, but periumbilical pain and vomiting persisted. The bowel movements remained the same. On the third hospital day he complained of severe, steady abdominal pain a few centimeters to the left of the umbilicus. This was not crampy and not increased with respirations. He had vomited milky material once and greenish material once earlier in the day, and had had one bowel movement. On examination the abdomen was soft and flat, with tenderness to the left of the umbilicus, and there was suggestive evidence of generalized peritoneal irritation. A few peristaltic tinkles were heard. Rectal examination was negative. The temperature was 97.6°F. and the pulse 100.

The blood hemoglobin was 22 gm. per 100 cc., and the white-cell count 37,000, with 89 per cent neutrophils. Plain films of the abdomen in the supine and erect positions revealed a moderate amount of gas in the large bowel from the level of the sacrum to the splenic flexure. The cecum showed the greatest distention. Several dilated loops of small bowel were observed below the transverse colon. There was no free air in the peritoneal cavity. A stool specimen was guaiac negative. Later the same day abdominal tenderness was slightly increased to the right of the umbilicus; peristalsis was absent, and there was slight abdominal distention. A Levin tube was passed, but no gas recovered. On the following day the patient complained of generalized pain in the left side of the abdomen. On examination there was diffuse, left-sided abdominal tenderness but no striking rebound or indirect tenderness. Peristalsis was absent. The temperature was normal and the pulse 100. The rest of the examination was as before; he did not have chest pain. A stool specimen gave a ++ guaiac test, as did the gastric drainage. An electrocardiogram showed some digitalis effect, but there was no evidence of extension of the myocardial infarct.

Later the same day an operation was performed.

Differential Diagnosis

Dr. John Stoeckle*: This sixty-six-year-old man certainly had coronary-artery disease in view of the clinical description of the chest pain and the electrocardiographic evidence of an acute myocardial infarction. He also had polycythemia vera in view of the fact that he had a hemoglobin of 21 gm. per 100 cc. and an elevated hematocrit and red-cell count. The leukocytosis is also consistent with this diagnosis, and yet it is also possible to interpret it as a result of the acute myocardial infarction. Again, I think it was polycythemia vera rather than secondary polycythemia since there was nothing to suggest chronic lung disease or congenital heart disease of the cyanotic type. Another possible explanation for an elevated red-cell count and hematocrit in the presence of nausea and vomiting is an apparent polycythemia from dehydration. The information given does not suggest that this extracellular-fluid loss over a three-week period accounted for this degree of polycythemia.

The abdominal pain is the main problem. However, I might get some findings out of the way before I discuss that problem. The urinary specific gravity of 1.019, the ++ test for albumin and the granular and hyaline casts I shall assume to have been due to some degree to benign nephrosclerosis. He had hypoalbuminemia—albumin of 3.2 gm. per 100 cc. One might interpret this as being due to renal disease and the nutritional failure of his present illness. The ++ edema of the legs in a patient who had had a recent myocardial infarction naturally makes me think of congestive heart failure. We do not have the findings that might corroborate this, such as a diastolic gallop, accentuated pulmonic second sound and venous distention. We do know there was prominence of the left ventricle on fluoroscopic examination. We are also told that he had had venous disease in the legs eleven years before admission, and the edema in the legs may have represented some degree of stasis, along with some factor due to the hypoalbuminemia. The prominent veins over the upper trunk and the generalized dusky hue, I think, are compatible with polycythemia. I do not believe one would have to consider such esoteric events as thrombosis of the portal vein with the development of the collateral venous drainage in the vena-cava system and the prominent cutaneous vessels. There is a real plethora in polycythemia vera.

Before I discuss the problem of abdominal pain I should like to ask Dr. Hanelin if any more information can be derived from the x-ray films than was given in the protocol.

Dr. Joseph Hanelin: I do not think they contain any more information than has already been given to you.

Dr. Stoeckle: I am interested in the Graham test.

Dr. Hanelin: A single nonopaque stone is present in a poorly functioning gall bladder. The chest examination shows no significant cardiac enlargement. There are rather prominent linear markings in both lungs, without any obvious edema and no increase in pleural fluid. The gastrointestinal examination reveals a hiatus hernia; otherwise, there is no intrinsic abnormality. There is an extrinsic pressure upon the duodenum at the junction of the first and second portions superiorly. An upper jejunal loop lies to the right of the midline so that some thought was given to the possibility of malrotation, but no true malrotation is present.

Dr. Stoeckle: How do you know that?

Dr. Hanelin: A barium-enema examination performed elsewhere before admission showed the colon to lie in normal position.

Dr. Stoeckle: Is this a finding that one normally sees?

Dr. Hanelin: The position of the jejunal loop is of no particular importance here; the distribution of the small bowel is subject to considerable variation. Three days after admission, probably at the time the abdomen became distended, films show a fair amount of gas in the large bowel. There are a number of slightly dilated small-bowel loops in the upper abdomen. One day later there is still a moderate amount of gas in the large bowel and also in some upper loops of small bowel, but the distention seems somewhat less than that observed on the preceding day. The statement in the protocol that the barium-enema study done in the other hospital was negative is not a true quotation of the note in the record, which stated that, although no obvious trouble was apparent in the films taken outside the hospital, it would be well to repeat the examination. Information obtained from the fluoroscopic

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examination is an essential part of the examination of the colon.

DR. STOECKLE: Has barium filled the small bowel down to the ileum?

DR. HANELIN: I should say that it has probably reached the upper ileum; about half the small intestine is filled with barium.

DR. STOECKLE: Is the defect related to the gall bladder?

DR. HANELIN: I think the gall bladder is lateral to the defect. The spleen appears slightly enlarged.

DR. STOECKLE: The splenomegaly would be consistent with the polycythemia. Now that I have all the information from the x-ray films I might summarize the nature of the abdominal disease as I see it. There was apparently a five-week history of intermittent pain in the periumbilical region, which suggests to me small-bowel origin of the pain. In addition, there was a history of nausea and vomiting of bile containing small-bowel and probably gastric contents, which suggests that, if there was an obstruction, it was below the entrance of the common duct. Moreover, the stools had changed somewhat in character, which does not seem to be specific for anything. Foamy, frothy, foul-smelling stools suggest some disturbance in bowel motility and absorption. The flecks of blood on the toilet paper, in view of subsequent guaiac-negative examinations, I attribute to anal bleeding rather than to a factor in the abdominal pain. We also know that before the operation the clinical picture changed. The pain, which I have attributed to the myocardial infarct, went away and abdominal pain of increasing severity developed. In addition, there was a severe leukocytosis, without fever, and more signs of abdominal distention and tenderness and guaiac-positive stools. I interpret this as evidence of peritoneal irritation, gangrene of the bowel and ileus.

There are a number of conditions that this man may have had. First of all I shall exclude volvulus of the jejunum from the fact that there was no good evidence of malrotation of the gut. In view of the pain and the presence of gallstones I shall consider an acute pancreatitis. We make this diagnosis most often in patients who have taken large amounts of alcohol or in patients with biliary-tract disease. The pain, however, is usually epigastric although it has certainly been periumbilical. These patients present themselves with the problem of disturbed gastrointestinal function. The diagnosis is made quite precisely by the finding of an early elevation of serum amylase. The clinical course is variable, depending on the extent and severity of the inflammatory process in the pancreas itself. By and large, the patients usually have acute symptoms with improvement. Here, there was progression of symptoms, without any confirmatory findings.

Another possibility is gallstone ileus. I do not think that all this patient's history can be interpreted as biliary-tract disease, though it is commonly said that biliary-tract disease may mimic coronary-artery disease even to changes in the electrocardiogram. The changes in the electrocardiogram in biliary-tract disease are not those of acute myocardial infarction. If he had biliary-tract disease, therefore, he had in addition coronary-artery disease. Although I think that gallstone ileus is a possibility, I should expect a story of right-upper-quadrant pain, usually a previous gallbladder attack, and, of course, if a stone was discharged into the small bowel, a symptom-free period before the stone became lodged somewhere in the terminal ileum and produced obstructive symptoms.

For the moment I do not have any explanation for the finding of extrinsic pressure on the first portion of the duodenum. When I read the protocol I thought that the pressure was probably from the gall bladder because in this region it overlies the duodenum.

The next consideration, since I think that this man had small-bowel disease, is intussusception, caused by a small-bowel tumor or Meckel's diverticulum. The finding of a greatly elevated white-cell count, without fever, and the positive guaiac reactions, both on the gastric aspiration and in the stool, suggest either infarction or an inflammatory reaction within the bowel. Either condition may certainly follow intussusception, with gangrene, intraluminal bleeding and some degree of obstruction, which may have been present subacutely all along.

An ulcer in a Meckel diverticulum is another possible explanation. Then one might consider that the terminal episode was a perforation; yet I do not think the clinical evidence bears this out. Patients with ulcers in Meckel diverticulums are more commonly said to have melena with or without abdominal pain. I should have to search hard to explain the constant, recurrent abdominal pain and the leukocytosis by means of this condition unless the ulcer had perforated, with abscess formation. The findings do not support this.

The final considerations are thrombosis or an embolism of one of the mesenteric arteries. I have assumed all along that this patient had a myocardial infarction so that he was a candidate for a mural thrombus on the endocardium of the left ventricle from which a fragment possibly broke off and entered one of the mesenteric arteries. This complication usually occurs rather late, not in the first few days after infarction. Certainly, I should not think that would explain all the recurrent abdominal pain, but it would explain the sudden episode followed by rapid development of shock. Mesenteric thrombosis, however, is a real possibility, particularly in view of the polycythemia, with which there is a tendency for thromboses to develop in various parts of the venous and arterial tree. Usually, with mesenteric thrombosis, the course is rapidly downhill, yet there have been reports of patients with recurrent bouts of abdominal pain associated with gastrointestinal upsets in whom the occlusion in the abdominal circulation is slow and is followed by sudden complete occlusion, with the development of classic findings—namely, some degree

of abdominal ileus, hemorrhage into the bowel and markedly elevated white-cell count, without much fever. The previously recurring abdominal pain could have been the phase of slow occlusion.

These are the main considerations in this patient and it seems to me difficult to be precise about which one it was. From the x-ray findings one cannot be certain about the presence of an intussusception, with perhaps gangrene and possibly perforation; because this patient certainly had a picture compatible with mesenteric thrombosis, although appearing rather late, I should favor the latter diagnosis. I believe the operation was to remove the segment of diseased bowel so that he might have some chance of survival. I have based all this on the facts that there was no evidence from the history or from the clinical findings of large-bowel disease and that this disorder was confined to the small bowel.

DR. J. FREYMANN: I wonder what you think about a dissecting aortic aneurysm and rupture into the aortic lumen?

DR. STOECKLE: I think that is a possibility; I forgot to mention that this patient's pain was described as noncrampy, and usually with small-bowel disorders one would expect some degree of crampy abdominal pain. It was in the region where an abdominal aneurysm is found, and one would expect to find something by physical and x-ray examinations. I do not see anything on the films to suggest that, nor would it account for the blood in the gut terminally unless the aneurysm had ruptured into the bowel lumen. The rupture usually occurs higher up.

CLINICAL DIAGNOSIS

Mesenteric thrombosis.

DR. JOHN STOECKLE'S DIAGNOSES

Polycythemia vera.
Mesenteric thrombosis, with gangrene of small bowel.

ANATOMICAL DIAGNOSES

Polycythemia vera.
Hemorrhagic infarction of sigmoid, venous.
Mesenteric thrombosis, venous.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Dr. Menendez assisted Dr. Robert R. Linton at the operation. He will tell us about the operation.

DR. CHARLES V. MENENDEZ: From the time of admission this man had had vague abdominal findings that were considered due to polycythemia. The day he was operated on it became apparent that a change had occurred: he became very ill; the white-cell count rose to 40,000; and there were definite signs of peritoneal irritation. Some observers thought that there was a mass in the left lower quadrant. There was retroperitoneal tenderness, absence of peristalsis and a positive guaiac reaction on the stool. The guaiac reaction the night before was reported negative.

At operation a devitalized segment of sigmoid about 13 cm. in length was found. The sigmoid in this area was red, firm and swollen to three or four times the normal size. When the mesentery of this infarcted segment of bowel was divided black clots were noted coming out of the veins. There was some bleeding from a few small arteries. Because of the poor condition of the bowel it was decided not only to resect the involved sigmoid but also to perform a proximal colostomy. I should like to emphasize the fact that the appearance of the remaining bowel was poor even after the devitalized segment had been removed. One observer at the operating table said that the patient had no chance of survival because of the bluish discoloration of almost the entire gastrointestinal tract.

DR. CASTLEMAN: The piece of sigmoid that we received was gangrenous owing to the venous thrombosis. I do not suppose it was the mesenteric vein primarily that had caused this but the sigmoidal veins.

DR. MENENDEZ: After the operation the patient did well for a while. The same symptoms recurred several days later, and he was again taken to the operating room. The small bowel was found to be gangrenous and was resected; an end-to-end anastomosis was made. Now he has 30 to 60 cm. of proximal jejunum with about 10 cm. of terminal ileum. The course since the second operation has been gradually downhill, and there is only a slight chance that he will recover.

DR. BERNARD M. JACOBSON: It is well to note that many persons have hemoglobin values of 16 gm. per 100 cc. in whom it is difficult to know whether that level represents early polycythemia or normal blood. I think it is a good policy to hold such persons under observation and to have blood counts done every six months to determine whether polycythemia is present, and to follow the definitive diagnosis of polycythemia with appropriate therapy.

I should like to add that the spleen was felt by two or three physicians. Concerning the hematocrit of 59 per cent it must be remembered that in the laboratory in which the test was done hypertonic anticoagulants are used; therefore, that hematocrit corresponds to one of about 65 per cent, which is very high.

When I saw the patient, unlike Dr. Stoeckle, I considered the various abdominal diseases that are complications of polycythemia. The classic complications are duodenal ulcer, possibly with hemorrhage, and mesenteric thromboses. By the time I saw the patient it was obvious that intestinal obstruction was present, and the story became quite clear. By that time it was impossible to do anything to rectify the thrombosis or decrease the platelets; his condition was too critical to permit any type of corrective definitive therapy aimed at the polycythemia.

Addendum. The patient died two and a half weeks after the second operation. Post-mortem examination showed extensive thrombosis of the portal, splenic, mesenteric, femoral and pelvic veins, as well as a generalized peritonitis.

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PHYSIOLOGY OF ANXIETY

ALTSCHULE'S paper, "Ideas of Eighteenth-Century British Medical Writers about Anxiety,"* published in the *Journal* last year, indicated that, although the present era may be called the Age of Anxiety, even the Garden of Eden was not untouched by this ubiquitous emotion. According to Altschule's investigations, there is probably today no greater intensity of human anxiety than at many previous times, but there is a greater preoccupation with the nature of it. Anxiety has become an object of anxiety.

The paper referred to above may be considered as a philosophical and historical prelude to Altschule's present progress report, published elsewhere in this issue of the *Journal*, on the true as well as the hypothetical content of anxiety — the stuff that bad dreams are made on. Recounting as it does the most recent steps taken to bring the popular concept of psychosomatic medicine within the bounds of scientific acceptance, it represents one of the most reasonable attempts yet made to re-fuse the fissionable material of which physiology and psychology are jointly composed.

It is a matter of observation, Altschule notes, that "many of the somatic changes that occur in association with spontaneous anxiety closely resemble various clinical and physiologic effects of the hormone." Thus, under such a unique heading as "Pharmacology of Anxiety," he shows that subjects given epinephrine by injection become anxious and that the administration of hexamethonium, which prevents the reflex liberation of epinephrine, prevents at least that anxiety that is caused by hypoglycemia. This effect may be observed even in patients with anxiety neurosis.

The establishment of conditioned reflexes is usually accelerated in anxious subjects or those susceptible to anxiety, and "learning" is accelerated in anxious persons when stress can be avoided by learning, or "with respect to simple tasks with high associative content." Otherwise, it is retarded.

Because of age-old observations on the relation between emotion and diseases of unknown etiology, the idea seems long to have been entertained that emotion has been the sole or chief cause of such diseases. It is a conclusion that more than a few psychiatrists of the present day have accepted without question, although the matter is not so simply settled. Complex factors are involved, and there is always danger of putting the cart before the horse If the complexity of these relations were doubted, one need only consider the bioelectric phenomenon cited by Altschule "that varied with emotion in man and with phases of the moon in man and in elm, oak and maple trees in New Haven." Lunacy may be well named, in New Haven as elsewhere.

*Altschule, M. D. Ideas of Eighteenth-Century British medical writers about anxiety. *New Eng. J. Med.* 248:646-648, 1953.

The time is coming when these factual researches will help more and more in an understanding of the relations between mind and matter and vice versa. Meanwhile, re-education and redirection, based on the individual's insight into his difficulties of adjustment is essential if his anxieties are to be met head on and brought under control. Inner conflicts must be kept under the control of inner resources, as the latter are developed; fortitude is needed to tolerate frustration. "My shadow is always with me," according to the song, "wherever I may go." It must also be remembered that shadows cannot exist without light — and that even platitudes, when the more original material that Altschule presents is unavailable, may serve an inspirational and consequently therapeutic purpose.

ERYTHROMYCIN-RESISTANT STAPHYLOCOCCI

In the two years since the results of the first clinical trials were reported,[1,2] erythromycin has been in wide use. Much of the popularity that it achieved was probably due to the increasing prevalence of staphylococci that are highly resistant to penicillin and other widely used antibiotics but sensitive to erythromycin. However, the likelihood that with widespread use this new agent might share the fate of its predecessors and lose its effectiveness against staphylococcal infections was anticipated from one of the first studies.[2,3] The rapid development of erythromycin resistance in staphylococci during exposure to this agent in vitro was readily demonstrated, and mention was made of 2 cases of endocarditis in which the resistance to erythromycin increased greatly during a few days of treatment.

The epidemiologic and clinical significance of the extensive use of erythromycin in establishing resistant strains of staphylococci within a hospital was dramatically demonstrated in a study reported by Lepper and his co-workers,[4] from the Municipal Contagious Hospital in Chicago. Among personnel who were carriers, the proportion of strains of staphylococci that were not inhibited by 100 microgm. per cubic centimeter or less of erythromycin increased from 0 to 75 per cent over a five-month period. This phenomenon occurred while the drug was being employed more frequently than any other agent in the treatment of patients. After the administration of erythromycin was discontinued, the frequency of resistant strains among the carrier personnel dropped to approximately 35 per cent. Concurrent with the increasing prevalence of resistant strains among the hospital personnel, similarly resistant strains of staphylococci infecting the tracheas of patients after tracheotomy rose from 0 to 95 per cent in a three-month period. As the organisms became more resistant, erythromycin became less effective in preventing or eradicating infections.

Similar, though perhaps less striking, observations were recently reported from the Mayo Clinic.[5] During the first two years of the use of erythromycin, workers there encountered 37 patients who had infections with erythromycin-resistant staphylococci among an estimated 1000 patients who had been treated with this antibiotic. Although this may appear to be a relatively low prevalence of resistant strains, it is apparent that infections with such resistant organisms have increased considerably — from 5 cases in the first year to 32 cases in the second year under study. Moreover, in 25 of the 37 patients, the initial staphylococcus isolated from the patients and tested was found to be already resistant to erythromycin, whereas no resistant strains had been encountered between December, 1952, and March, 1953. In most cases the infection with resistant organisms appeared to be due to crossinfection or to transmission by carriers among hospital personnel. The possibility of transmission was considered likely in 24 of the 37 patients; the resistant staphylococci were present in infections of the bowel, urinary tract and postoperative wounds.

How to prevent or combat this trend remains a serious problem. The possibility of avoiding, delaying or depressing the emergence of erythromycin-resistant strains by the use of that agent in combination with other effective antibiotics has been demonstrated in vitro[6] and has been confirmed to some extent in the treatment of patients.[7] It should be clear, however, that erythromycin, like other antibiotics, should not be given except with clear indications, and the possibility of resistant staphylococci during its administration should always be borne in mind, irrespective of the nature of the infection under treatment. Prolonged use of erythromycin alone should be avoided under all circumstances.

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UNCRABBED AGE

At the beginning of the summer the gerontologists met at the Harvard School of Public Health while June roses were blooming across the way, to consider the problems of life's December. Some months be-

fore, the new geriatrics unit at the School had looked hard and long at its collective resources and had found — scarcely to its surprise — few clear-cut answers to the problems of aging. More significantly, there were few indisputable definitions, even of the aging process itself. It was time to ask the right questions.

Deliberately, the School set up its first conference on problems of aging to thresh out a few fundamentals: "Who Are the Aging?" "What Is Aging?" "What Are the Needs?" "How Do We Provide a Complete Program of Medical Care for the Older Patient?" and "Where Does the Health Team Fit in the Gerontologic Picture?"

From Wednesday, June 9, to Saturday, June 12, the groups conferred, at 55 Shattuck Street by day, and at the Jimmy Fund Auditorium by night. Participants of panels and work groups ranged from Boston's own world-famed clinicians to legislators, nationally distinguished names in the medical specialties, devoted nurses, social workers and the newest crop of students specializing in public health at Harvard.

To well thatched, unwrinkled readers, superbly confident that *they* will not alter with the years, the Conference gives corroboration, of a sort. The human personality, prize jewel in the crown of *Homo sapiens,* merely becomes more itself as it goes along. Man is continuously distilled, it seems, into a concentrated essence of himself.

Paul Dudley White's one-hundred-and-four-year-old patient, chipper Charles W. Thiery, highlighted (and delighted) the clinical session of the Conference. Mr. Thiery, whose last serious illness was pneumonia — a hundred and two years ago — sports a brisk cane and a bright eye as he walks his customary miles each day. To queries by Dr. White regarding probable reasons for his exceptional longevity, the twinkling Thiery replied: "Well, I have never been married, but I don't *think* that's the reason!"

More relevant than bachelordom, for the attainment of a healthy old age, is the quantity (not the quality) of illness that may afflict one. As Dr. White emphasized, a diagnosis of coronary-artery disease may be nothing, in itself. The consistently unmarried Mr. Thiery, who retired from goldsmithing at ninety-two, has also been consistently, though mildly, dyspeptic and nervous (even nervousness does not necessarily shorten one's life, Dr. White points out), and he still likes to talk.

The motif of the unchanging but more highly concentrated personality has an important bearing on several areas of gerontology. For instance, the old folks should not be isolated in housing units far from all other age groups. Total segregation is both unintelligent and cruel. Special units with built-in safety features that are equally applicable to all ages may be constructed for old people, if these units are incorporated as a part of larger projects, where the residents may have as much contact as they wish with younger people and children.

Another finding of the Conference on Aging was notably demonstrated by Mr. Thiery: aging can be a *healthy* process (just as Dr. Howard F. Root emphasized the antithesis, showing, in his diabetic patient, a twenty-four-year-old woman with the physiologic changes usually found in the aged). An old man or woman is not doomed to be, minute by minute or month by month, a *sick* old man or old woman. The interrelations of chronic disease and the aging process are far less closely joined, it appears, than observers have frequently assumed.

Gerontology — the broad study of the aging and the aged — does not always wear, one is happy to note, the sober face long imputed to its component, geriatrics.

HENRY K. OLIVER PROFESSOR OF HYGIENE

In June Dr. Arlie V. Bock, for more than thirty years on the staff of Harvard University and for nearly twenty years Henry K. Oliver Professor of Hygiene, retired from his post with the honorary degree of Doctor of Science. During his occupancy of this chair he had maintained and increased the prestige and importance envisioned for it by its founder and established by his predecessors, Dr. Roger I. Lee and the late Dr. Alfred Worcester.

Dr. Bock's successor was announced in August, and there is no question regarding the quality of service that this department will continue to deliver. Dr. Dana L. Farnsworth goes to Harvard from the Massachusetts Institute of Technology, where he has been for eight years the first full-time medical director. Born in 1905, he received an A.B. degree in 1927 and a B.S. degree in 1931 from West Virginia University, and his degree in medicine from Harvard Medical School in 1935. His career since that time has been in college health, for after an internship at the Massachusetts General Hospital he accepted an appointment as assistant director of health at Williams College in 1935, becoming director in 1945. The following year he received his appointment at Technology, where he served also as acting dean of students in 1950 and 1951.

Dr. Farnsworth held the rank of commander in the Navy during World War II, part of the time as a medical officer on the hospital ship *Solace* in the South Pacific. He is a diplomate of the American Board of Psychiatry and Neurology, a fellow of the American Psychiatric Association and a past president of the American College Health Association.

Dr. C. C. Coxe, of Easton, Md., recently performed the operation of amputating the leg at the hip-joint, with complete success.

Boston M. & S. J. *Sept. 20, 1854*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, October 6, at 10:30 a.m. This meeting will be followed by the Cotting Luncheon.

Business:

1. Call to order at 10:30 a.m.
2. Presentation of record of meeting held May 17, 1954, as published in Vol. 251, Supplement No. 1, July 22, 1954, of the *New England Journal of Medicine*.
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.
Secretary

DEATHS

ADAMS — Edward E. Adams, M.D., of West Roxbury, died on August 12. He was in his forty-third year.

Dr. Adams received his degree from Boston University School of Medicine in 1937. He was a fellow of the American Medical Association and secretary of the West Roxbury Medical Association.

He is survived by his widow, four daughters, his mother and a sister.

CLAP — Edmund W. Clap, M.D., of Boston, Massachusetts, and Norwich, Vermont, died on August 6. He was in his eighty-fifth year.

Dr. Clap received his degree from Harvard Medical School in 1898. He was a member of the New England Ophthalmological Society.

DEACY — John J. Deacy, M.D., of Methuen, died on July 25. He was in his sixty-sixth year.

Dr. Deacy received his degree from Tufts College Medical School in 1913. He was formerly medical examiner, Essex County, assistant city physician and physician, Board of Health, Lawrence. He was a member of the Surgeons' Club, Rochester, Minnesota, and the staff, Bon Secours Hospital, Methuen.

He is survived by a son, two grandchildren, a sister and a brother.

BOSTON MEDICAL LIBRARY

THE WELLCOME HISTORICAL MEDICAL LIBRARY

The story of the Burroughs Wellcome Company and the Wellcome philanthropies, the trust in support of research, and the Historical Medical Museum and Library was told in the *London Times* supplement of August 25, 1953, and has been reissued in pamphlet form by the Foundation.[1]

The Wellcome Historical Medical Library, in London, under the supervision of its new librarian, Mr. F. N. L. Poynter, has begun the publication of a quarterly indexing periodical[2] dealing with the history of medicine and science. The material is arranged in two classes: subject and personal or biographic.

Mr. Poynter has compiled a catalogue of the fifteenth-century books and pamphlets in his library, and it has been published by the Oxford University Press.[3]

The arrangement of the titles, the format and the printing are well done in every way. There are all the necessary indexes, including one on subjects, and the price is moderate. The director of the Boston Medical Library, while in London last year, had the exceptional opportunity of examining closely the collection under the guidance of the former librarian, Mr. William Bishop.

The centennial of Sir Henry Wellcome, who was born in Wisconsin in 1853, was celebrated last year and was the occasion of an editorial in the *Journal* of December 3.

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

THE LEMUEL SHATTUCK HOSPITAL

The construction of the Lemuel Shattuck Hospital has been completed and it will be opened to receive patients in September, 1954. The hospital is located at 170 Morton Street, Jamaica Plain 30, Boston, Massachusetts, with the main entrance off Circuit Drive in Franklin Park. The Lemuel Shattuck Hospital has a normal bed capacity for 600 patients, and it is designed for the medical and surgical care of patients with chronic diseases and will act as a nucleus for the development of prevention, teaching and research in chronic diseases.

FUNCTIONS OF THE HOSPITAL

It will provide *specialized facilities* for the diagnosis and treatment of patients suffering from chronic diseases and cancer who may potentially benefit from such hospitalization. The types of cases to be cared for will be all cases of chronic illness that may be helped by medical or surgical treatment and are capable of rehabilitation. Patients will not be accepted for custodial care, domiciliary care or terminal care, but the intent is to hospitalize those patients with chronic dis-

cases or cancer early so that the development of the progress of these diseases may be controlled, and that by early treatment these citizens may retain their economic usefulness to the community for as long a time as possible. Upon completion of hospitalization patients will be referred back to their own physicians, other institutions or out-patient clinics, including the hospital's own Out-Patient Department.

The hospital will serve as a *center of training* in chronic illness; that is, a teaching hospital affiliated with the three medical schools in Boston and Harvard School of Public Health; a teaching hospital for resident physicians; and a school for practical nurses. It will also be affiliated for teaching purposes with schools of physical medicine, occupational therapy and social service.

The hospital will serve as an active *center for research* in chronic diseases and cancer, concerning cause, prevention and cure.

The hospital will have a large *out-patient clinic* for patients with chronic diseases. The utilization of the Out-Patient Department, it is hoped, will prevent hospitalization of some cases of chronic illness and also will provide a more rapid turnover of bed patients if there is an assurance that the patients may return for regular out-patient therapy. The Out-Patient Department will also aid in a more complete research in chronic diseases.

The hospital will provide a complete *rehabilitation service* for the disabled and chronically ill, including research in improved methods of rehabilitation and professional training of doctors, nurses, physiotherapists and other professional personnel in this field.

Admission Requirements

To meet the admission requirements, a patient must be suffering from a chronic illness that can be helped by medical or surgical treatment, and that is capable of rehabilitation.

Upon written application of a registered physician, the Department of Public Health may admit as a patient to the Lemuel Shattuck Hospital, for the treatment of chronic diseases, subject to such rules and regulations as the Department may prescribe, any person residing in the Commonwealth for at least two years within the period of three years immediately prior to date of such application. Any such patient may be discharged from said hospital either upon his own request or upon determination of the Department, but not otherwise. (Chapter 111, General Laws, Sections 68, 68A, 68B, 68C and 68D.)

All applications for admission shall be sent directly to the hospital.

Rates

1. Total charges when paid by patient — up to $7.50 per diem.
2. Total charges when paid by city or town — $7.50 per diem.
3. For out-patient examination — no charge.
4. For out-patient medical or surgical treatment — $3.00 per treatment.
5. For out-patient x-ray therapy — $3.00 per treatment up to eight treatments; for nine or more treatments a flat charge of $25.00 for the series.
6. For out-patient physical therapy treatment — $1.00 per treatment.
7. For out-patient accident cases — only first aid treatment will be given, and the patient referred to a general hospital. Charges $5.00 plus any surgical supplies used.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1954

RÉSUMÉ

Disease	July 1954	July 1953	Seven-Year Median
Chancroid	1	6	2
Chicken pox	380	439	475
Diphtheria	1	2	6
Dog bite	1665	1450	1404
Dysentery, bacillary	12	92	9
Encephalitis, infectious	4	1	2
German measles	116	124	121
Gonorrhea	165	171	213
Granuloma inguinale	0	0	0
Hepatitis, infectious	64	74	6†
Lymphogranuloma venereum	0	0	0
Malaria	4	6	6
Measles	2303	102	616
Meningitis, meningococcal	5	3	5
Meningitis, Pfeiffer bacillus	0	2	2
Meningitis, pneumococcal	0	2	2
Meningitis, staphylococcal	0	1	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	6	3	3
Mumps	955	614	442
Poliomyelitis	55	67	30
Salmonellosis	24	25	7
Scarlet fever	106*	71	119
Syphilis	138	195	173
Trichinosis	1	5	3
Tuberculosis, pulmonary	143	250	221
Tuberculosis, other forms	9	14	14
Typhoid fever	0	0	3
Undulant fever	1	2	3
Whooping cough	161	126	130

*Includes streptococcal sore throat.
†Five-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, German measles and scarlet fever.

The few reported cases of diphtheria and scarlet fever maintain the unusually low levels reached in the past three years.

Diseases above the seven-year median were bacillary dysentery, infectious hepatitis, measles, mumps, poliomyelitis and salmonellosis.

The drop in cases of infectious hepatitis reported is not significant. There is no indication that the number of cases reported will fall much below the all-time high reached last year.

The cases of measles reported this year remain high. This is at least partially a result of the all-time low incidence of last year. Mumps, on the other hand, is up in spite of the relatively high incidence of 1953.

The monthly reports of whooping cough indicate a definite tendency toward an increased incidence over 1953.

The increase in the July, 1954, poliomyelitis cases over the seven-year median is not significant, but it is definitely lower than the July, 1953, figure.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Gardner, 1.
Dysentery, amebic: Boston, 1.

Dysentery, bacillary: Boston, 9; Brockton, 1; Melrose, 1; Northampton, 1; total, 12.

Encephalitis, infectious: Holyoke, 1; Lowell, 1; Newton, 1; Seekonk, 1; total, 4.

Hepatitis, infectious: Bedford, 1; Belchertown, 2; Billerica, 2; Boston, 10; Brockton, 2; Cambridge, 3; Chelsea Naval Hospital, 2; Dartmouth, 1; Fall River, 13; Fort Devens, 1; Gardner, 1; Greenfield, 1; Hudson, 1; Lowell, 1; Longmeadow, 1; Lynn, 4; Mendon, 1; Needham, 1; Newton, 1; Norton, 1; Plymouth, 2; Quincy, 1; Reading, 1; Somerset, 2; Somerville, 1; Swampscott, 1; Taunton, 1; Webster, 1; Worcester, 4; total, 64.

Malaria: Cambridge, 1; Fort Devens, 1; Lynn, 1; Murphy Army Hospital, 1; total, 4.

Meningitis, meningococcal: Attleboro, 1; Boston, 1; Marshfield, 1; Needham, 1; Somerset, 1; total, 5.

Meningitis, mumps: Weymouth, 1.

Meningitis, undetermined: Attleboro, 1; Fort Devens, 2; Mansfield, 1; Milford, 1; Stoneham, 1; Worcester, 1; total, 7.

Poliomyelitis: Ashland, 1; Bedford, 2; Beverly, 1; Boston, 1; Boylston, 1; Danvers, 2; Dartmouth, 1; Falmouth, 1; Fitchburg, 3; Holliston, 1; Marblehead, 1; Natick, 1; New Bedford, 1; Newburyport, 2; Newton, 1; Norton, 1; Oxford, 1; Paxton, 1; Swampscott, 1; Wakefield, 1; Worcester, 10; total, 35.

Psittacosis: Framingham, 1.

Salmonellosis: Boston, 3; Brookline, 1; Cambridge, 1; Fall River, 2; Lawrence, 1; Medford, 2; Milford, 1; Newton, 2; Peabody, 1; Quincy, 1; Tewksbury, 1; Upton, 6; Wakefield, 1; Worcester, 1; total, 24.

Trichinosis: Milford, 1.

Undulant fever: Plymouth, 1.

CORRESPONDENCE

UNITED STATES SAVINGS BONDS

To the Editor: I should like to call the attention of your readers to the opportunity presented for the purchase of Series E and Series H United States Savings Bonds.

The Series E bond, which has been on sale since 1941, is an appreciation bond, bought for three fourths of its maturity value, maturing in nine years and eight months at face value, paying 3 per cent if held to maturity, and having an extension period of an additonal ten years after its maturity, during which period it pays 3 per cent interest.

The Series H bond is an income-paying bond, purchasable at par, paying interest semiannually by Treasurer check, always redeemable at par, likewise maturing in nine years and eight months with a yield of 3 per cent if held to maturity, and sold in denominations of $500 to $10,000.

Both these bonds offer absolute safety, and purchases are limited to $20,000 of each series in a given calendar year. If they are lost or destroyed, the Treasury will replace them, thus giving an added advantage.

At present, physicians are not eligible for social security, and the monthly purchase of either Series E or Series H bonds can be arranged through local banks. They can provide an important addition to any presently planned annuity or retirement program, with the great advantage that in the event of an emergency they may be redeemed on short notice.

ALDEN C. BRETT, *Chairman*
Massachusetts Savings Bonds
Advisory Committee

Boston

MEDICAL ASPIRATIONS

To the Editor: From my personal observations I have concluded that among all obvious indications for diagnostic paracentesis, that for pericarditis with effusion has long been least appreciated by medical men, particularly internists. Today, when exploratory aspiration is common, fatal errors as a result of its omission still occur in spite of positive x-ray evidence of fluid.

Fellow interns of mine from 1910 to 1912 not only performed all the clinical laboratory work but also had to obtain by aspiration blood serum from the hearts of rabbits for treatment of certain dyscrasias. We were chagrined whenever any of us inadvertently killed an animal.

GILBERT W. HAIGH, M.D.

Worcester, Massachusetts

NOTICES

MASSACHUSETTS HEART ASSOCIATION

A special meeting of the Massachusetts Heart Association will be held in the Morse Auditorium, Museum of Science, Science Park, Boston, on Friday, September 24, at 8 p.m. Dr. Gustav Nylin, professor of medicine, University of Stockholm, Sweden, will speak on the subject "Circulation in Brain and Heart" (a preliminary report of studies with thorium-B-labeled erythrocytes, with Dr. Hans Bloemer).

Interested physicians, medical students and members of the New England Postgraduate Assembly are cordially invited to attend. (Emergency telephone number: RIchmond 2-1410.)

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The Clinical Assembly of the Massachusetts Academy of General Practice will be held on Wednesday, September 22. Dr. Harry C. Solomon, superintendent and medical director of the Boston Psychopathic Hospital, will be host. He will be assisted by Drs. Robert W. Hyde, assistant superintendent, Milton Greenblatt, director of research, and Elvin V. Semrad, clinical director and Mr. Francis Macomber, recreational director. The morning session will be held in the auditorium of the Boston Psychopathic Hospital, 74 Fenwood Road, Boston, and the afternoon and evening sessions at the Hotel Statler.

PROGRAM

10:00 a.m.	Welcome and introductory remarks about the Boston Psychopathic Hospital.
	Discussion by a group of patients concerning hospital care and treatment.
	Psychodrama: group therapy with patients.
	Demonstration of electric-shock therapy.
	Lobotomy—case presentation.
	Demonstration of a staff meeting.
12:30 p.m.	Registration.
1:30 p.m.	Luncheon (Parlor A, Hotel Statler).
2:30 p.m.	Doctors, Dollars and Workmen's Compensation. Laurence S. Locke, LL.B., of Lynn, Massachusetts, assistant editor-in-chief, *NACCA Law Journal*.
3:30 p.m.	Physiology of the Colon. Morton J. Oppenheimer, M.D., professor of physiology, Temple University School of Medicine.
	Practical Discussion of the Rectum and Colon for the General Practitioner. Howard D. Trimpi, M.D., associate professor of proctology, Temple University School of Medicine.
4:30 p.m.	Annual meeting.
5:30 p.m.	Cocktail and social hour (Bay State Room, Hotel Statler).
	Dancing (Ken Reeves Trio).
7:00 p.m.	Dinner.
8:00 p.m.	Evening speaker: John S. Detar, M.D., Milan, Michigan, Speaker of the House, Congress of Delegates, American Academy of General Practice.

MASSACHUSETTS HOSPITAL SCHOOL

An all-day symposium on the subject "Total Rehabilitation of the Handicapped Child" will be presented at the Massachusetts Hospital School, Canton, Massachusetts, on Saturday, November 6, at 10:00 a.m. The principal speaker will be Alfred R. Shands, Jr., M.D., medical director of the Alfred I. duPont Institute of the Nemours Foundation.

PAN-AMERICAN ACADEMY OF GENERAL PRACTICE

The sixth congress of the Pan-American Academy of General Practice will be held in Lima, Peru, February 11 to 25, 1955. The meeting will be held jointly with the Pan-American Association of Medical Specialties and the Latin-American Congress of Physical Medicine.

Reservations should be made through Dr. Arturo Martinez, Secretary, Pan-American Academy of General Practice, 54 East 72d Street, New York 21, New York.

M & R PEDIATRIC RESEARCH CONFERENCE

The thirteenth M & R Pediatric Research Conference will be a symposium on adrenal function in infants and children, under the auspices of the Department of Pediatrics, State University of New York, Upstate Medical Center, and will be held in the auditorium, State University of New York, College of Medicine at Syracuse, November 3 and 4. All interested persons are invited.

HARTFORD MEDICAL SOCIETY

The program for the coming year of the Hartford Medical Society is as follows:

October 4. Some Aspects of the Anemias. Dr. Ovid O. Meyer.
October 18. Lesions of the Vulva. Dr. John Parks.
November 1. Renal Function. Homer W. Smith.
November 15. Cardiac Arrhythmias: Mechanisms and method of treatment. Dr. Harry Gold.
December 6. Rheumatic Fever. Dr. T. Duckett Jones.
December 20. Chemotherapy of Cancer. Dr. Alfred Gellhorn.
January 3. The Value of a Sense of Humor. Samuel Ramsey.
January 17. Common Endocrine Problems in Gynecology. Dr. Charles Lee Buxton.

The above lectures will be held in the Hunt Memorial Building, Hartford.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The nineteenth annual convention of the National Gastroenterological Association and the first annual convention of the American College of Gastroenterology will be held at the Shoreham, Washington, D. C., October 25-27.

The sixth annual course in postgraduate gastroenterology, under the direction of Drs. O. H. Wangensteen and I. Snapper, will be given at the Shoreham and Walter Reed Army Medical Center Hospital, October 28-30. Further information may be obtained from the National Gastroenterological Association, 33 West 60th Street, New York 23, New York.

AMERICAN COLLEGE OF SURGEONS

The fortieth annual clinical congress of the American College of Surgeons will be held in Atlantic City, New Jersey, November 15 to 19. Drs. Alan Gregg and Robert H. Kennedy, of New York, will be the speakers at the opening evening session.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 17–28. Consultation Clinics for Crippled Children in Massachusetts. Page 362, issue of August 26.
SEPTEMBER 21. South End Medical Club. Page 451, issue of September 9.
SEPTEMBER 21. New England Hospital House Officers Club. Page 451, issue of September 9.
SEPTEMBER 22. Massachusetts Academy of General Practice. Fall Clinical Assembly. Page 495.
SEPTEMBER 22. New England Pediatric Society. Page 968, issue of June 3.
SEPTEMBER 22–24. Mississippi Valley Medical Society. Page 246, issue of August 5.
SEPTEMBER 23. American College of Physicians Telecast. Page 451, issue of September 9.
SEPTEMBER 23–25. Industrial Health Conference. Page 364, issue of August 26.
SEPTEMBER 24. Massachusetts Heart Association. Page 495.
SEPTEMBER 24. American Medical Writers' Association. Page 246, issue of August 5.
SEPTEMBER 27–DECEMBER 8. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.
SEPTEMBER, 1954–APRIL, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.
SEPTEMBER 30–OCTOBER 2. Canadian Society for the Study of Fertility. Page 285, issue of August 12.
OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.
OCTOBER 4, 1954–JANUARY 17, 1955. Hartford Medical Society. Notice above.
OCTOBER 6. Massachusetts Medical Society. Stated Meeting of the Council. Page 493.
OCTOBER 7 and 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.
OCTOBER 8. New England Society of Anesthesiologists. Hanover, New Hampshire.
OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.
OCTOBER 11–15. American College of Physicians Course. Page 44, issue of July 1.
OCTOBER 16–22. American Occupational Therapy Association. Page 1092, issue of June 24.
OCTOBER 18–29. New York Academy of Medicine Graduate Fortnight. Page 44, issue of July 1.
OCTOBER 22. National Vitamin Foundation Symposium. Page 410, issue of September 2.
OCTOBER 25–27. New England Postgraduate Assembly. Hotel Statler, Boston.
OCTOBER 25–27. National Gastroenterological Association. Notice above.
OCTOBER 25–30. Course in Care of Atomic Casualties. Page 285, issue of August 12.
OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.
OCTOBER 27–29. International Symposium on the Hypophyseal Growth Hormone. Page 1092, issue of June 24.
OCTOBER 29. Massachusetts Public Health Association. Fall Meeting. Blake's Restaurant, Springfield, Massachusetts.
OCTOBER 31–NOVEMBER 4. American Institute of Dental Medicine. Page 968, issue of June 3.
NOVEMBER, 1954–MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
NOVEMBER 2–5. Fourth Annual Bay State Rehabilitation Conference. Hotel Statler, Boston.
NOVEMBER 3 and 4. M & R Pediatric Research Conference. Notice above.
NOVEMBER 3–5. National Society for Crippled Children and Adults. Page 44, issue of July 1.
NOVEMBER 6. Massachusetts Hospital School Symposium. Page 495.
NOVEMBER 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.
NOVEMBER 15–19. American College of Surgeons. Notice above.
NOVEMBER 15–26. Laboratory Diagnosis of Tuberculosis Course. Page 246, issue of August 5.
DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.
DECEMBER 8. New England Pediatric Society. Page 968, issue of June 3.
DECEMBER 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.
JANUARY 3–MAY 9. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.
JANUARY 10–15, 1955. Course in Care of Atomic Casualties. Page 285, issue of August 12.
FEBRUARY 7–9. McIntyre Saranac Conference. Page 410, issue of September 2.
FEBRUARY 11–25, 1955. Pan-American Academy of General Practice. Notice above.
MARCH 7–12, 1955. Course in Care of Atomic Casualties. Page 285, issue of August 12.
MAY 4 and 5, 1955. American Psychosomatic Society. Page 286, issue of August 12.
JUNE 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 23

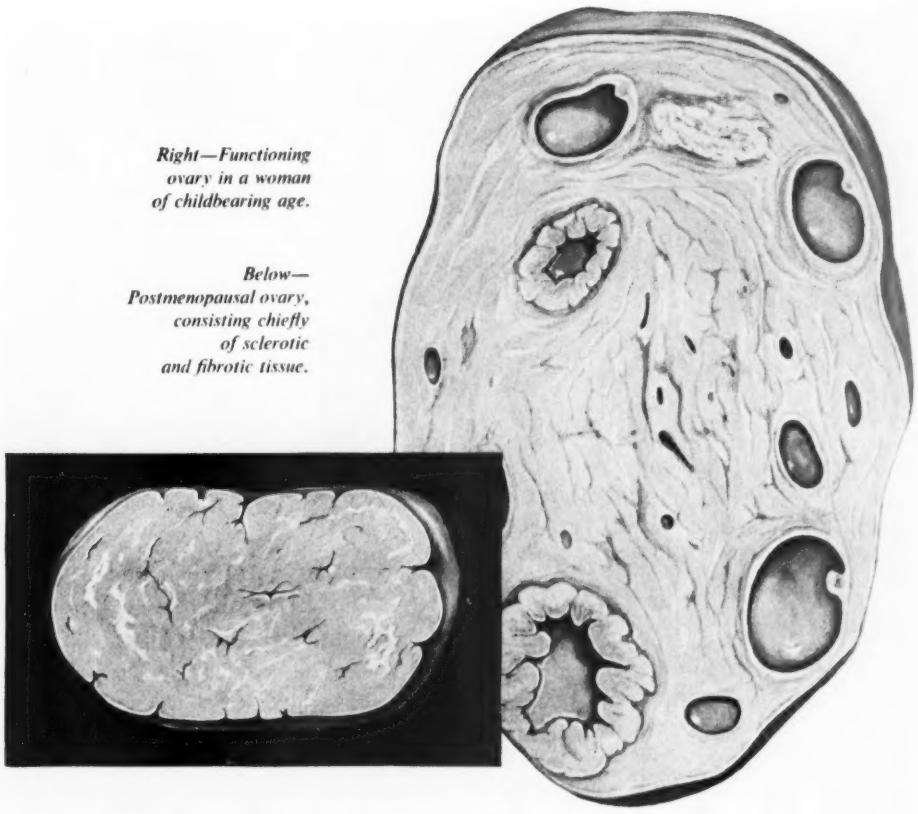
THURSDAY, SEPTEMBER 23

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*10:00–11:00 a.m. Surgical Rounds. 5th floor teaching unit, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:00 a.m. Thoracic Conference. Clinical Applications of Right and Left Heart Catheterization. Dr. Dwight E. Harken and Dr. Lewis Dexter. Main Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.

(Notices concluded on page xxxi)

Right—Functioning ovary in a woman of childbearing age.

Below—Postmenopausal ovary, consisting chiefly of sclerotic and fibrotic tissue.



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[1]Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestril, New England J. Med. *247*:829 (Nov. 27) 1952.

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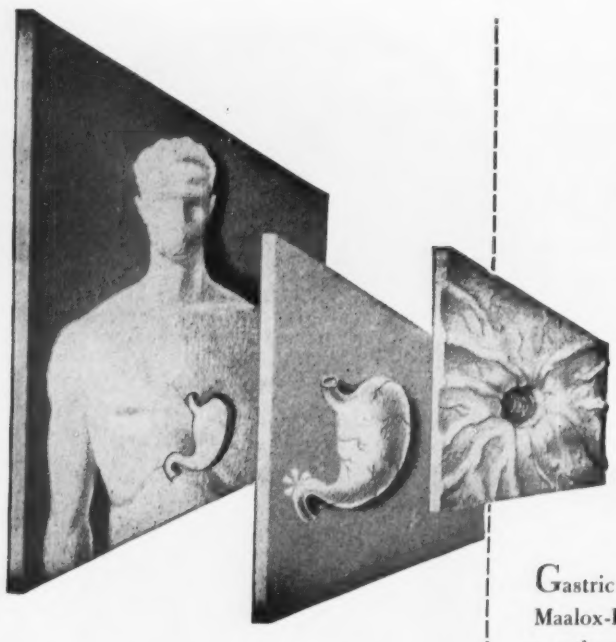

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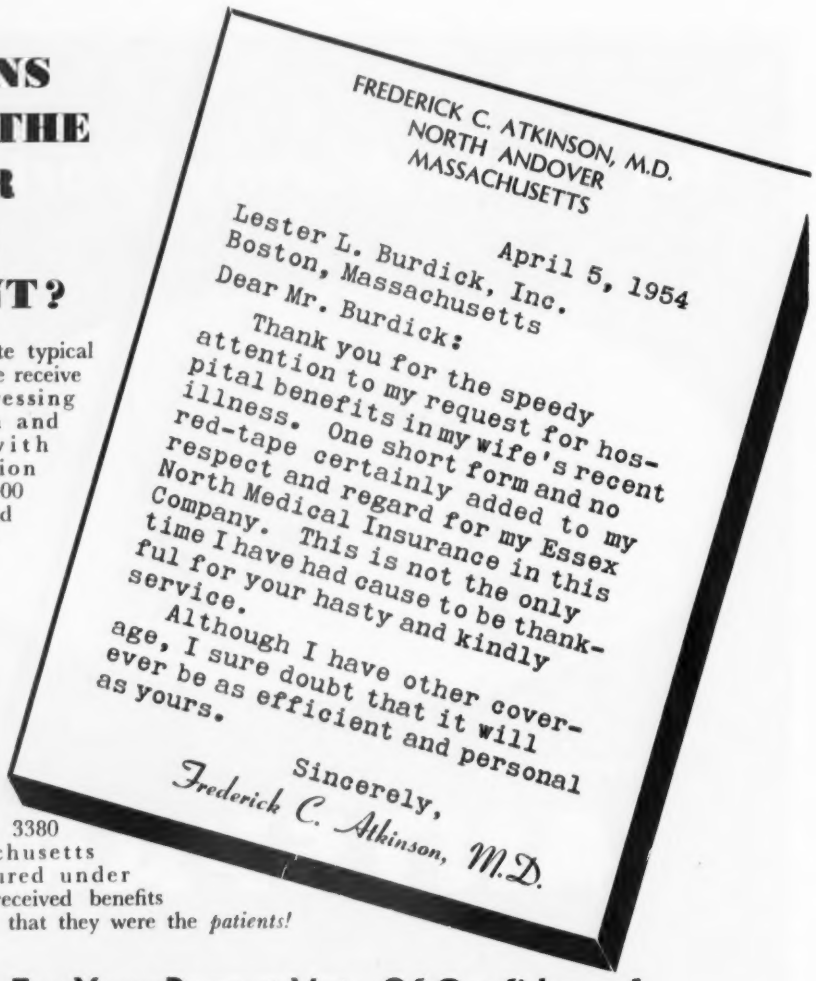

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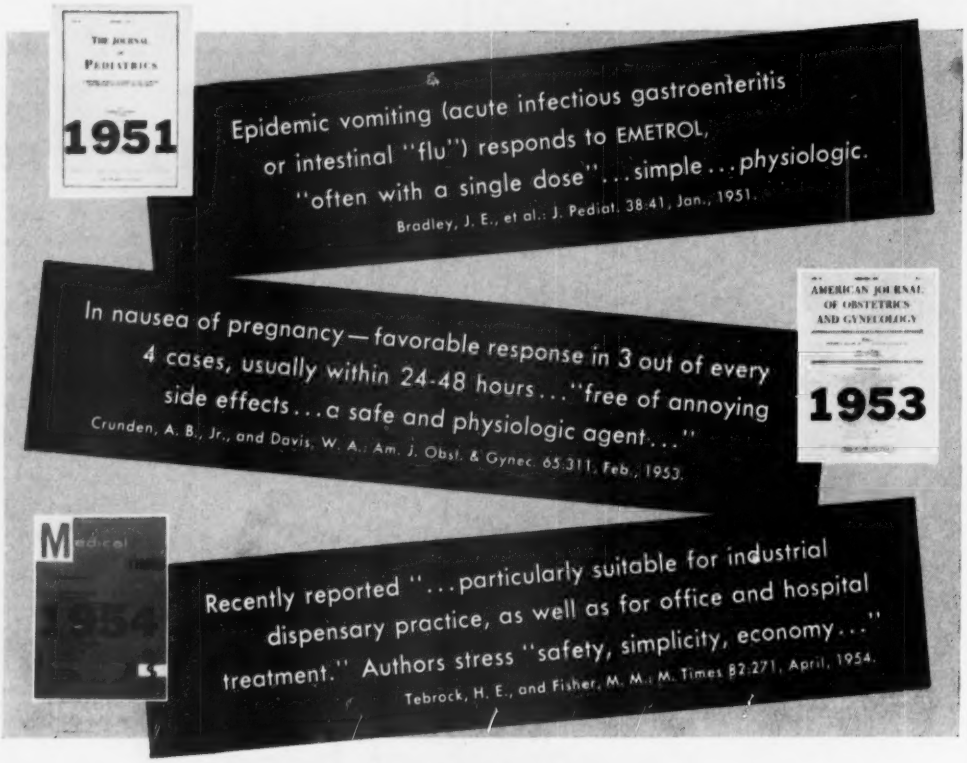
THE JOURNAL OF PEDIATRICS
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Epidemic vomiting (acute infectious gastroenteritis or intestinal "flu") responds to EMETROL, "often with a single dose"... simple... physiologic.
Bradley, J. E., et al.: J. Pediat. 38:41, Jan., 1951.
In nausea of pregnancy—favorable response in 3 out of every 4 cases, usually within 24-48 hours..."free of annoying side effects...a safe and physiologic agent..."
Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, Feb., 1953.
AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY
1953
Medical Times
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Recently reported "...particularly suitable for industrial dispensary practice, as well as for office and hospital treatment." Authors stress "safety, simplicity, economy..."
Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, April, 1954.

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†Fromer, J. L., and Cormia, F. E.: J. Invest. Dermat. 18: 1, 1952.

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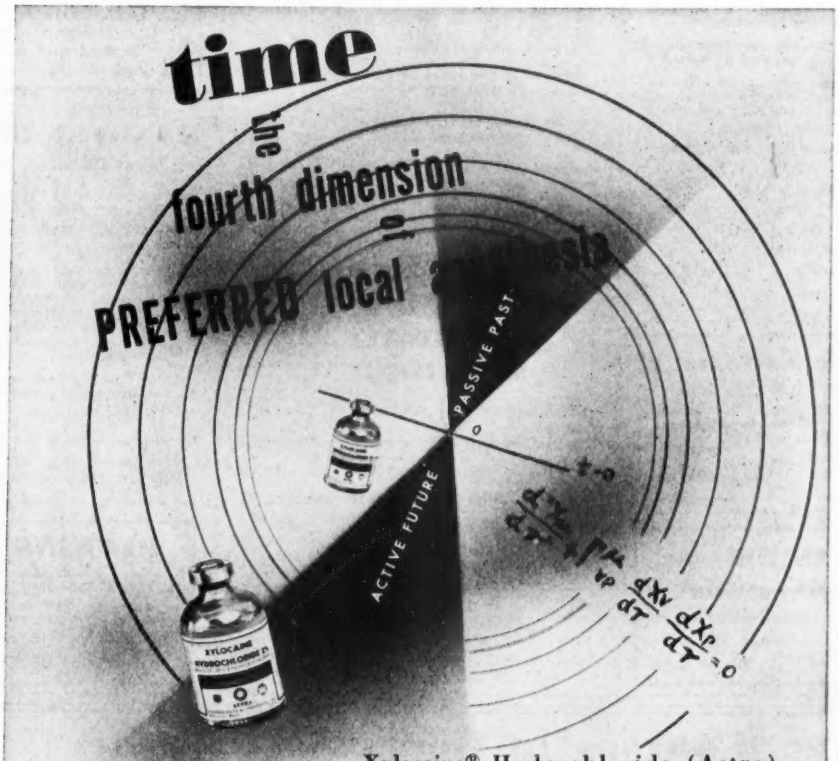

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3:15—Disintegration Test begins in actual stomach fluids (pH 2.7). Beaker at left contains ordinary enteric-coated erythromycin. At right is new FILMTAB ERYTHROCIN Stearate (Erythromycin Stearate, Abbott).

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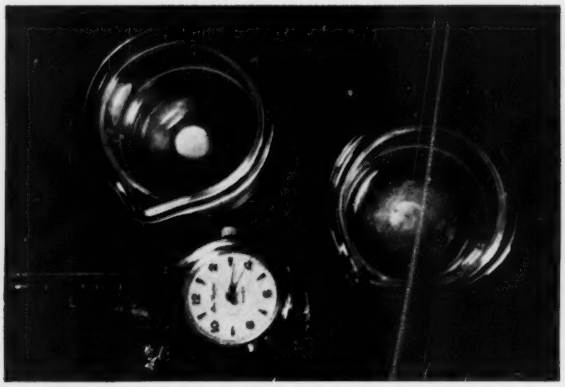
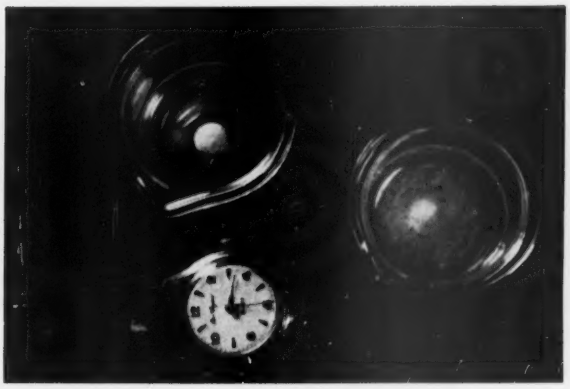
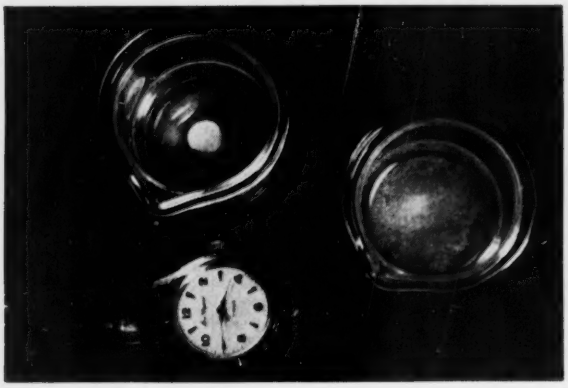


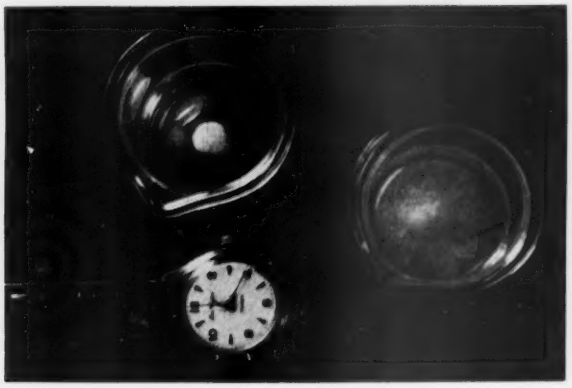
3:20—Five minutes later, *Filmtab** coating has already started to disintegrate. The tissue-thin film actually begins to dissolve within 30 seconds after patient swallows tablet.



3:30—*Filmtab** is now completely dissolved. At this stage, ERYTHROCIN is ready to be absorbed, and ready to destroy sensitive cocci—even those resistant to other antibiotics.



3:45—Now the *Filmtab** tablet mushrooms out with all of the drug available for absorption. Note that enteric-coated tablet is still intact. Tests show that the new Stearate form definitely protects ERYTHROCIN against gastric acids.



4:00—Because of *Filmtab** (marketed only by Abbott) the drug is released faster, absorbed sooner. In the body, effective ERYTHROCIN blood levels now appear *in less than 2 hours* (instead of 4-6 hours as before). Abbott

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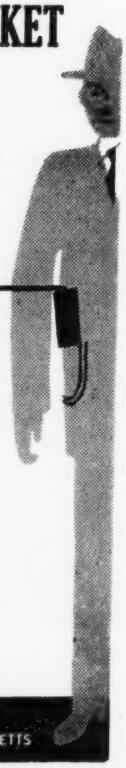

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NOTICES *(Concluded from page 496)*

FRIDAY, SEPTEMBER 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Mortality and Morbidity Meeting. Dr. J. McGonigle. St. Margaret's Hospital, Dorchester.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*8:00 p.m. Massachusetts Heart Association. Morse Auditorium, Museum of Science, Science Park, Boston.

SATURDAY, SEPTEMBER 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, SEPTEMBER 27

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

TUESDAY, SEPTEMBER 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. New England Deaconess Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*5:00–6:00 p.m. Medical Management of the Pregnant Diabetic. Dr. Francis L. Colpoys. St. Margaret's Hospital, Dorchester.

WEDNESDAY, SEPTEMBER 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th floor teaching unit, Beth Israel Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. Out-Patient Department.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

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